University of Alberta

Outcomes Associated with Antidiabetic Agents in Patients with Diabetes and Heart Failure

by

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requirements for the degree of Doctor of Philosophy

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Abstract

Controversy exists surrounding the impact of antidiabetic therapies in people with heart failure and diabetes. Historically, there has been limited evidence to guide clinical decisions in people with comorbid heart failure and diabetes. Thus, the overall objective of this program of research was to systematically evaluate the effects of antidiabetic agents on morbidity and mortality in patients with heart failure and diabetes. This objective was accomplished through three related studies: 1) an observational study on the use of metformin in people with heart failure and diabetes; 2) a systematic review of antidiabetic therapies and outcomes in people with heart failure and diabetes and; 3) a pilot clinical trial evaluating the use of metformin or placebo in people with heart failure and diabetes.

Evidence from the observational study and the systematic review suggest that metformin is the only antidiabetic agent not associated with measurable harm and, in fact, may be associated with improved outcomes in people with heart failure and diabetes. Importantly, however, all of the evidence was based on observational studies. Thus, to overcome this limitation we designed and implemented a pilot randomized controlled trial. The trial was terminated early, however, due to poor availability of suitable patients. Surprisingly, a high number of individuals were excluded for using high dose metformin; suggesting that clinical equipoise does not exist and metformin is being used as a critical component of the glucose lowering regimen in people with heart failure and diabetes.

In carrying out this clinical research, a second major outcome was the development of a methodology that may improve the validity and interpretation of composite outcomes commonly used in observational and randomized controlled trial

research. We demonstrated how quality adjusted survival analysis can adjust for the potential unequal impact of the components of the composite outcome on a patients' health, thereby providing a more transparent assessment.

Our program of research provides important evidence for the front line clinician who is initiating or modifying antidiabetic regimens. It also highlights the need for new methodologies in clinical research to provide a clearer picture of the potential benefits or harm associated with therapeutic interventions.

Dedication

To *Jeff Johnson*, my friend, mentor and supervisor. I am grateful for the guidance and friendship you have provided over the years. Although it was a long journey, you always ensured that it progressed smoothly. I have learned so much knowledge from you during this time not only in research but also in personal and professional skills. My hope is that someday in the future I can provide to my trainees and staff the same level of supervision, support, and kindness that you have provided me all these years. It is a chapter in my life that I will look back on with fond memories and I look forward to the many chapters that lie head both as your friend and colleague.

To the members of my thesis committee, *Sumit Majumdar, Ross Tsuyuki, and Finlay McAlister* (in no particular order I might add!). You have all been great friends and mentors over the years and I will undoubtedly continue to rely on your friendship, expertise, and knowledge for many more years to come. I would not have been able to complete this work without all of the valuable information and clinical guidance you have provided me. Although there were many emails that raised my blood pressure over the years, they were always for the best. I look forward to the many years of working with you. I now know, however, that if a response starts with a 'tilt of the head' from Me2, a 'Sure, but…' opening from Finlay, or a 'I guess…' response from Ross that it is unlikely that the difference of opinion will come out in my favour!

To my family, thank you for all of your support and always pushing me to chase after my dreams.

Lastly and most important, I would like to thank *Michelle*. You and the Rikki have always been there and supported me throughout all of these years. I could not have done any of this without your understanding and caring. There we many days when I thought I would never see the light at the end of the tunnel but you were always there to brighten my day and help push me along. I know you have sacrificed both personally and professionally for me to chase down my dreams. I hope you know how much it has meant to me and how important you are to me. Love ya!

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CHAPTER 1: INTRODUCTION

1.1 Statement of the Problem

1.1.1 Diabetes Mellitus

Diabetes mellitus is a common progressive metabolic disease characterized by chronic hyperglycemia.[1] Although the exact number of people affected by the disease is not known, it is estimated that 135 million people are affected with the disease worldwide.[2] In Canada, there are currently over 2 million Canadians affected with this condition and the number is expected to increase to 3 million by the year 2010.[3] The burden on the health care system to treat and manage these patients is considerable. A person with diabetes incurs medical costs that are two to five times higher than those of a person without diabetes.[3] Although there has been little research into the total economic cost of treating diabetes in Canada, a recent study indicated that the direct medical and indirect (lost productivity) costs of diabetes and its complications in Canada for 1998 was between $4.76 - $5.23 billion (in U.S. dollars).[4]

The development of diabetes is associated with significant short and long term health complications due to microvascular and macrovascular complications of the disease. In particular, the impact of macrovascular complications is significant and is the leading cause of morbidity and mortality in people with diabetes. Consequently, it is not surprising that diabetes is a major risk factor for the development of cardiovascular diseases, including stroke, hypertension, and heart and vascular disease. The incidence of, and mortality from, cardiovascular disease and stroke is 2-3 times higher for men and 3-4 times higher for women with diabetes as compared to the general population.[5-8]

1.1.2 Heart Failure

Although often forgotten, heart failure is a serious and common comorbidity of diabetes. One of the first studies to establish a link between diabetes and heart failure was the Framingham Heart Study. In this study, the incidence of heart failure was twofold higher in diabetic men and fivefold higher in diabetic women as compared to non-diabetic counterparts, irrespective of coexisting coronary artery disease or

hypertension.[9] Numerous studies have since shown diabetes to be a strong risk factor for the development of diabetes.[10-19] For example, a large observational study using the Kaiser Permanente databases showed that patients with diabetes were twice as likely to have either prevalent or incident onset heart failure as compared to their non-diabetes counterparts.[11] More recently, pooled data from 31,546 high-risk patients participating in two international trials suggests that for every 1 mmol/L increase in fasting blood glucose, there is a 10% increased risk for heart failure related hospitalizations.[12] Other evidence also supports the notion that poor glycemic control is associated with increasing risk of heart failure with the risk increasing by 10 to 15 percent for every 1 unit increase in A1c.[10,20,21]

Although the true prevalence of comorbid diabetes and heart failure is not known, approximately 25% of patients enrolled in major heart failure clinical trials had diabetes.[14] Moreover, population based studies, which may provide a more valid estimate due to less concerns of selection bias, have suggested 30 to 40 percent of patients with heart failure also have diabetes.[22-25] Moreover, it has also been suggested that these estimates may be higher when the most recent diagnostic criteria for diabetes are used.[14,26]

It is also well known that the presence of diabetes is associated with a poor clinical prognosis in heart failure patients. Results from large heart failure trials indicates patients with diabetes have higher rates of hospitalization and mortality as compared to patients without diabetes.[27,28] In the studies of left ventricular dysfunction (SOLVD) trials and registry, the presence of diabetes was associated with a 29% increased risk of mortality and a 52% increased risk of mortality or hospitalization for heart failure as compared to patients without diabetes.[27] Other studies have also shown diabetes to be a strong predictor of morbidity or mortality in patients with heart failure.[13,17,18,29-33] Although studies have suggested that patient factors may influence the risk of mortality associated with diabetes in heart failure (e.g., sex, ischemic or nonischemic heart failure), diabetes is still an important predictor of morbidity and mortality in patients with heart failure.[34]

1.1.3 Antidiabetic Agents in Heart Failure

The adverse effects of hyperglycemia in patients with diabetes are well known.[35-37] As a result, normalization of blood glucose levels is one of the fundamental aspects of any management program for diabetes as it has clearly been shown to reduce microvascular complications.[36,37] More recently, there is also evidence that chronic hyperglycemia is associated with an increased risk for cardiovascular morbidity and mortality.[38,39] Although there is limited evidence, the benefits of tight glycemic control would be expected to apply to people with heart failure and diabetes.[34]

Historically, only insulin, sulfonylurea, and metformin were available to control hyperglycemia in patients with diabetes. Over the last decade, however, new classes of oral antidiabetic agents and insulin analogues have become available to the clinician to control patients' hyperglycemia. Unfortunately, pharmacologic management of hyperglycemia in patients with existing heart failure posses a significant challenge to the clinician. Of the currently available therapies, metformin is considered "absolutely" contraindicated and thiazolidinediones are "relatively" contraindicated in patients with heart failure.[40] Thus, only sulfonylureas, acarbose, and insulin therapy remain as options; however, acarbose is associated with high rates of intolerance,[40] and insulin is associated with much reluctance on the part of patients and providers. Moreover, insulin therapy has also been associated with an increased risk of heart failure and may be associated with poorer outcomes.[9,11,31] Importantly, there is limited evidence for any of the currently recommended antidiabetic agents in people with heart failure.

Further complicating the issue, early evidence has also suggested that tight glycemic control may actually be associated with increased mortality in patients with diabetes. In the only study completed to date, Eshaghian *et al.* found that in patients with diabetes and advanced heart failure (n=123), those with A1c≤7% were at a much greater risk of mortality compared to those with A1c values >7% (hazards ratio 2.3; 95%CI 1.0-5.2%).[41] Although the reason for these findings are unclear, several proposed explanations including the influence of the type of antidiabetic agents used in the study have been proposed.[34]

1.2 Summary

Cardiovascular disease is the leading cause of morbidity and mortality in patients with diabetes. Moreover, the proportion of cardiovascular disease attributable to diabetes has increased significantly over the last few decades.[42] It should not be surprising, therefore, that diabetes is a major independent risk factor for the development of heart failure. Moreover, comorbid diabetes and heart failure is associated with significantly poorer outcomes compared to either disease alone. As a result, the best evidence-based interventions must be undertaken in this population to reduce the burden of these diseases.[34] Despite clear evidence of benefit of antidiabetic agents in people with diabetes, their impact in people with comorbid heart failure is far less certain. It is therefore imperative that better evidence is generated on how to optimally control blood glucose levels in patients with diabetes and heart failure.

1.3 Objectives

The objectives of this program of research were: 1) to evaluate the use of metformin compared to other antidiabetic agents on outcomes in people with heart failure and diabetes; 2) to systematically review the relationship between antidiabetic therapies and outcomes in people with heart failure and diabetes and; 3) to illustrate the use of an advanced survival analysis method that incorporates the impact of therapeutic interventions on patients' health related quality of life in people with diabetes and/or heart failure.

1.4 Program of Research

A series of four papers contributed to the overall study goals. The first study (Chapter 2) evaluated the use of metformin in people with heart failure and type 2 diabetes. This involved an observational study using the Saskatchewan Health databases to evaluate the effect of metformin compared to sulfonylurea therapy on all-cause hospitalization or mortality in a broad patient population of new users of oral antidiabetic agents with incident onset heart failure. The second study (Chapters 3) involved a systematic review and meta-analysis of the mounting evidence for the use of oral antidiabetic agents or insulin in patients with heart failure and diabetes. Specifically, the

impact of antidiabetic agents on all-cause mortality or hospitalization was assessed. Subsequent to these studies, a pilot study (Chapter 4) was designed and implemented, PHANTOM (Patients with Heart Failure ANd Type 2 Diabetes Treated with Placebo Or Metformin), to evaluate the feasibility of a large randomized controlled trial of metformin in patients with heart failure and type 2 diabetes. The final study (Chapter 5) illustrates how health related quality of life can be incorporated into survival analysis to improve composite outcome assessment for both observational and randomized controlled trials. For this study, we reanalyzed two previously reported studies, our observational study of metformin in people with heart failure and diabetes (i.e., Chapter 3) and a randomized controlled trial, the Digitalis Investigation Group (DIG) study.

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CHAPTER 2: IMPROVED CLINICAL OUTCOMES ASSOCIATED WITH METFORMIN IN PATIENTS WITH DIABETES AND HEART FAILURE*

2.1 Abstract

Objective – Metformin is considered contraindicated in patients with heart failure due to concerns over lactic acidosis, despite increasing evidence of potential benefit. The aim of this study was to evaluate the association between metformin and clinical outcomes in patients with heart failure and type 2 diabetes.

Methods - Using the Saskatchewan Health databases, 12,272 new users of oral antidiabetic agents were identified between the years 1991-1996. Subjects with incident HF (n=1,833) were identified through administrative records based on ICD-9 code 428 and grouped according to antidiabetic therapy: metformin monotherapy (n=208), sulfonylurea monotherapy (n=773), or combination therapy (n=852). Multivariate Cox proportional hazards models were used to assess differences in all-cause mortality, all-cause hospitalization, and the combination (i.e., all cause hospitalization or mortality).

Results – Average age of subjects was 72 years, 57% were male, and average follow-up was 2.5 (SD 2.0) years. Compared to sulfonylurea therapy, fewer deaths occurred in subjects receiving metformin: 404 (52%) for sulfonylurea monotherapy vs. 69 (33%) for metformin monotherapy [hazard ratio (HR) 0.70 (95% CI 0.54-0.91)] and 263 (31%) for combination therapy [HR 0.61 (95% CI 0.52-0.72)]. A reduction in deaths or hospitalizations was also observed: 480 (63%) for sulfonylurea monotherapy vs. 115 (55%) for metformin monotherapy [HR 0.83 (95% CI 0.70-0.99)] and 480 (56%) for combination therapy [HR 0.86 (95% CI 0.77-0.96)]. There was no difference in time to first hospitalization between study groups.

Conclusion – Metformin, alone or in combination, in subjects with HF and type 2 diabetes was associated with reduced morbidity and mortality compared to sulfonylurea monotherapy.

2.2 Introduction

Heart failure is common in patients with type 2 diabetes, and diabetes portends poorer outcomes in those with heart failure.[1-3] There is also evidence that chronic hyperglycemia is associated with an increased risk for cardiovascular morbidity and mortality.[4,5] However, clinicians treating heart failure in patients with type 2 diabetes find their options limited since metformin is considered "absolutely" contraindicated in such patients and thiazolidinediones are "relatively" contraindicated.[6] Thus, only sulfonylureas, acarbose, and insulin therapy remain as options; however, acarbose is associated with high rates of intolerance,[6] and insulin is associated with much reluctance on the part of patients and providers. Moreover, insulin therapy has also been associated with an increased risk of heart failure.[7,8] It is not surprising, therefore, that 10% of Medicare patients with heart failure and diabetes use metformin,[9] a practice repeatedly deemed "inappropriate".[9-11] Is the use of metformin in diabetic patients with heart failure truly inappropriate? Metformin improves glycemic control and other cardiovascular risk factors (such as lipids),[12-14] and in obese diabetic subjects, metformin reduces mortality.[15] In a large population-based observational study, we also demonstrated that use of metformin was associated with reduced risk for all-cause and cardiovascular-related mortality compared to sulfonylurea monotherapy.[16] Perhaps metformin is beneficial in patients with heart failure.

Although the contraindication to metformin arose over concerns about the *potential* for lactic acidosis and its relation to phenformin (another biguanide that was removed from market after 306 cases of lactic acidosis were reported in the 1970s), there is a paucity of evidence that actually links metformin with lactic acidosis.[17,18] Indeed, the near-absence of any cases of lactic acidosis in large observational studies and the fact that metformin levels do not correlate with lactate levels in those who do develop lactic acidosis supports the viewpoint that metformin may be "an innocent bystander" in sick patients rather than a causal agent.[19,20] As noted by Misbin, "the increased risk of lactic acidosis (attributable to metformin) is either zero or so close to zero that it cannot be factored into ordinary clinical decision making".[17] By corollary, two decades ago, beta-blockers were considered contraindicated in heart failure, and commonly accepted

'quality indicators' for the use of beta blockers explicitly stated that people with left ventricular dysfunction or heart failure were 'ineligible' for receipt of beta-blockers.[21] Numerous trials have since refuted these concerns and established beta-blockers as cornerstones in the treatment of heart failure.

Like beta-blockers, it could be that 'inappropriate' use of metformin in heart failure may actually be associated with improved outcomes relative to other antidiabetic therapies. Masoudi *et al.* recently described a large scale observational study suggesting metformin therapy was associated with reduced risk for all-cause mortality at one year in a hospitalized elderly Medicare population with heart failure and type 2 diabetes.[22] As all subjects were recently hospitalized with heart failure and were older than 65 years of age, it is uncertain if these benefits can be expected in a much broader, lower risk population of patients with heart failure and type 2 diabetes. Furthermore, given the short duration of follow-up (i.e., one year), it is unclear if these benefits might persist. We designed this study to examine outcomes, both short and long term, in a broad, unselected population based cohort of patients with heart failure and type 2 diabetes who are treated with metformin or other oral antidiabetic medications.

2.3 Methods

We analyzed data from the computerized databases of Saskatchewan Health. These databases have been described in detail elsewhere.[16,23,24] Briefly, Saskatchewan Health is a provincial government department providing universal health coverage for approximately 1 million people in Saskatchewan, Canada. Databases include the demographic and vital statistics, outpatient prescription drugs, hospital claims, and outpatient physician services. These databases have been used in numerous epidemiological studies evaluating safety of drug therapies and are considered to be both high-quality and comprehensive.[16,23-25]

First, we identified 12,272 new users of oral antidiabetic agents based on prescription claims between January 1, 1991 and December 31, 1996, who were aged 30 years or older, and who had health coverage and were eligible for drug benefits at least one year before the index prescription.[16,23] Federal employees (e.g., Royal Canadian Mounted Police), and inmates of federal penitentiaries, constituting about 1% of the

population, are not captured in these databases. In addition, registered Indians do not receive drug benefits from the province. Therefore, approximately 9% of the population is not included in this analysis.[16,23]

Then we identified those subjects with a record of a hospital stay or physician service for heart failure, based on ICD-9 code 428, between December 1, 1991 and December 31, 1999.[26,27] The index date for the diagnosis of heart failure was defined as the date of the first hospital or physician record. Those with prevalent heart failure (i.e., those with a hospital record for heart failure in the 3 years prior to starting oral antidiabetic agent) and/or those subjects who ever had prescription claims for insulin therapy were excluded. We then categorized new users of oral antidiabetic agents with incident heart failure into 3 mutually exclusive groups according to oral antidiabetic prescription claims throughout the follow-up period (i.e., January 1, 1991 to December 31, 1999): sulfonylurea monotherapy, metformin monotherapy, or combination therapy. Combination therapy was defined as any use of metformin and sulfonylurea therapy throughout the follow-up period. All subjects were prospectively followed until death, termination of Saskatchewan Health coverage, or December 31, 1999, providing a maximum follow-up of 9 years.

Our primary outcome was all-cause mortality, both at 1 year (i.e., short term) and by the end of the follow-up period (i.e., long term). Secondary outcomes were all-cause hospitalizations at 1 year and at the end of the follow-up period. We also evaluated the effects of antidiabetic therapy on a composite outcome commonly used in heart failure trials, namely all-cause hospitalization or all-cause mortality.[3]

Analysis

Using Cox proportional hazards regression models, unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated to assess the relationship between antidiabetic drug use and outcomes. The sulfonylurea monotherapy cohort served as reference group for all estimates. Potential confounding variables included in all multivariate models were age, sex, a modified Chronic Disease Score (CDS)[16,23], therapies known to affect heart failure outcomes [i.e., ACE inhibitors, angiotensin II blockers (ARBs), beta-blockers, antiplatelet agents, nitrates, lipid-lowering

therapies, antiarrhythmic agents, and spironolactone], and total physician visits prior to HF diagnosis. The CDS provides an indication of burden of concurrent comorbidities by identifying specific drug therapies during the follow-up period.[28-30] The CDS is well-validated, and higher scores are associated with increased mortality, hospitalization rates, and health resource utilization[28-30] and it has been shown to be comparable to other comorbidity indices.[31]

To adjust for potential selection bias we also calculated a "propensity score" using standard methods and included this as a covariate in all multivariate models.[32] The inclusion of the propensity score in the analysis made no significant difference in the HR point estimates obtained (i.e. < 1% change in point estimates) nor the width of confidence intervals, and because our basic findings were unchanged we present models without propensity scores. All analyses were conducted using SPSS version 12.

2.4 Results

Of the 12,272 new users of oral antidiabetic agents during the years of our study, 2,793 (23%) had a hospital or physician record for heart failure. Excluding the 625 cases of prevalent heart failure and the 335 subjects who were ever treated with insulin, we identified 1,833 eligible subjects with incident heart failure who were treated with oral antidiabetic agents. Of this cohort, 773 (42%) were treated with sulfonylureas alone, 208 (11%) with metformin alone, and 852 (47%) received both a sulfonylurea and metformin. The mean age of our cohort was 72 (SD 10.7) years, 57% were male, and mean follow-up was 2.5 (SD 2.0) years following the diagnosis of heart failure. The sulfonylurea group was slightly older, had fewer comorbidities, and had fewer prescription claims for heart failure-related medications as compared to either the metformin monotherapy or combination groups (Table 2.1).

All-Cause Mortality – One Year

At one year, compared to the 200 deaths in the sulfonylurea monotherapy group (26%), there were 29 deaths (14%, unadjusted HR 0.52, 95% CI 0.35-0.76) in the metformin monotherapy group and 97 deaths (11%, unadjusted HR 0.41, 95% CI 0.32-

0.52) in the metformin-sulfonylurea combination therapy group. After controlling for age, sex, CDS, drug therapies known to affect heart failure outcomes, and total physician visits before HF diagnosis, we found that metformin alone (adjusted HR 0.66, 95% CI 0.44-0.97) or in combination with other agents (adjusted HR 0.54, 95% CI 0.42-0.70) was associated with reduced one year all-cause mortality compared with sulfonylurea monotherapy in patients with incident heart failure (Table 2.2).

All-Cause Mortality – Longer Term

At the end of follow-up (mean 2.5 years, median 2.1 years), compared to the 404 deaths in the sulfonylurea monotherapy group (52%), there were 69 deaths (33%, unadjusted HR 0.63, 95% CI 0.49-0.82) in the metformin monotherapy group and 263 deaths (31%, unadjusted HR 0.50, 95% CI 0.43-0.58) in the metformin-sulfonylurea combination therapy group (Figure 2.1). In multivariate regression analyses, we found that metformin alone (adjusted HR 0.70, 95% CI 0.54-0.91) or in combination with other agents (adjusted HR 0.61, 95% CI 0.52-0.72) was associated with reduced all-cause mortality compared with sulfonylurea monotherapy (Table2.2; Figures 2.1 and 2.2).

Although they are not an endpoint of the study, we also evaluated cause-specific deaths. The numbers of cardiovascular-related deaths were 224 (55.4%) in the sulfonylurea monotherapy group, 36 (52.2%, adjusted HR 0.63, 95% CI 0.45-0.90) for metformin monotherapy, and 145 (55.1%, adjusted HR 0.58, 95% CI 0.47-0.72) in the combination therapy group. There was no significant difference with respect to diabetes-related deaths between the cohorts: 40 (9.9%) for sulfonylurea monotherapy, 3 (4.3%, adjusted HR 0.48, 95% CI 0.15-1.58) for metformin monotherapy and 28 (10.6%, adjusted HR 0.95, 95% CI 0.58-1.58) for combination therapy. Of the diabetes-related deaths, 6 deaths were attributed to hypoglycemia (2 in the sulfonylurea monotherapy group, none for metformin monotherapy, and 4 for combination therapy; $p>0.05$).

All-Cause Hospitalizations

At one year, compared to the 406 hospitalizations in the sulfonylurea monotherapy group (53%), there were 102 hospitalizations (49%) in the metformin monotherapy group and 435 hospitalizations (51%) in the metformin-sulfonylurea

combination therapy group. At the end of follow-up, there were 538 hospitalizations in the sulfonylurea monotherapy group (70%) compared to 143 hospitalizations (69%) in the metformin monotherapy group and 632 hospitalizations (74%) in the metformin-sulfonylurea combination therapy group. Multivariable analyses demonstrated no significant association between use of various oral antidiabetic agents and hospitalizations (Table 2.2).

Composite Outcome (all-cause hospitalization or all-cause mortality)

At one year, composite events occurred in 480 patients in the sulfonylurea monotherapy group (63%), with 115 events (55%, unadjusted HR 0.80, 95% CI 0.65-0.98) in the metformin monotherapy group and 480 (56%, unadjusted HR 0.82, 95% CI 0.72-0.93) in the metformin-sulfonylurea combination therapy group. At the end of follow-up, there were 658 deaths and/or hospitalizations in the sulfonylurea monotherapy group (85%) compared to 160 (77%, unadjusted HR 0.84, 95% CI 0.71-1.00) in the metformin monotherapy group and 681 (80%, unadjusted HR 0.83, 95% CI 0.75-0.93) in the metformin-sulfonylurea combination therapy group. After adjusting for the same covariates as in our other analyses, we found that metformin alone (adjusted HR 0.79, 95% CI 0.65-0.98) or in combination with other agents (adjusted HR 0.86, 95% CI 0.75-0.98) was associated with reduced one-year composite endpoints. At the end of the follow-up, adjusted HR (95% CI) for the composite endpoint was 0.83 (0.70-0.99) for metformin monotherapy and 0.86 (0.77-0.96) for combination therapy, compared to sulfonylurea monotherapy (Table 2.2).

2.5 Discussion

In our population of newly treated diabetic patients over the age of 30 years, the prevalence of heart failure was 23%, which is almost identical to the 22% reported in a nationally representative sample of Medicare claims in the US.[26] We found that heart failure patients with type 2 diabetes who used metformin (either alone or in combination with a sulfonylurea) had lower all-cause mortality rates than sulfonylurea users, even after adjusting for multiple confounding variables. Importantly, we also found that

metformin exposure was not associated with an increase in hospitalizations, supporting the premise that it appears to be safe in this vulnerable population. Moreover, there were no hospitalizations or deaths in any of the cohorts attributed to metabolic acidosis throughout the follow-up period.

Although an observational study such as ours cannot conclusively prove that an agent is efficacious, it can raise hypotheses that may or may not warrant a clinical trial. The first step in deciding whether an observational result mandates a clinical trial is to consider whether the finding is pathophysiologically sound. Is it plausible that metformin use in patients with diabetes and heart failure would reduce mortality? Metformin therapy has been shown to improve hyperinsulinemia in patients with type 2 diabetes.[33] It is therefore conceivable that through this action metformin therapy may be associated with improved outcomes in patients with heart failure and type 2 diabetes.[16] At the very least, our study suggests that metformin is not associated with an increased risk of adverse outcomes in heart failure patients when compared to sulfonylurea therapy (the most commonly prescribed oral antidiabetic agents, which increase endogenous insulin secretion and may be associated with adverse cardiovascular outcomes).[16,34,35]

The strengths of our study include the large unselected population based sample of subjects with heart failure and type 2 diabetes, comprehensiveness and quality of the databases used, the relatively long duration of follow-up, and the ability to control for the effects of comorbidities and drug therapies known to affect outcomes in patients with heart failure. In addition, it has been suggested that observational studies, such as ours, are the preferred method for examining issues related to medication safety in the real-world.[36]

There are also several limitations that need to be considered. First, we did not have access to data on subjects' glycemic control. Several observational studies have indicated that tight glycemic control may be associated with reduced risk of developing heart failure.[37,38] Furthermore, tight glycemic control also improves outcomes in patients with diabetes.[4,5,15,38] Although metformin is equipotent to sulfonylurea therapy in controlling blood glucose levels,[12] metformin therapy may have been utilized in subjects who were perceived to have 'less severe' diabetes compared to subjects in the sulfonylurea monotherapy group. If this was the case, however, we would have expected

to see higher mortality and hospitalization rates in the combination therapy group, since the use of combination therapy would suggest even higher glycemic levels or more severe diabetes.[33] The significant reduction in morbidity and mortality observed in the combination therapy group compared to the sulfonylurea monotherapy implies that glycemic control is not the sole explanation for our findings.

Second, our results may be attributed to selection bias in that physicians may have withheld metformin in subjects perceived to be at an increased risk of adverse events or death. However, we did adjust for those factors shown to be prognostic in heart failure (age, sex, comorbidities, and proven efficacious medications such as ACE inhibitors, beta-blockers, spironolactone, and antiplatelet agents), and we believe that by restricting our analysis to incident cases of heart failure, we minimized the possibility that there were important differences among patients. Moreover, metformin users had a higher number of comorbidities and would have been expected to have a greater, not lesser, risk of mortality. To address this issue further, we also conducted a propensity score analysis; this did not, however, alter the main effects or our study findings.

Third, we do not have any clinical or laboratory information on factors such as functional status, severity of heart failure, left ventricular function, or renal failure. The lack of renal function data is particularly important since it is an independent predictor of poor outcomes in heart failure.[2] Although it is possible that people in the metformin group had lower rates of renal failure, the fact that at least 40% of all patients with symptomatic heart failure have reduced renal function,[39] it is likely that a significant proportion of people in our study who were exposed to metformin would have had renal dysfunction.

Despite a lack of any high quality evidence, metformin is currently considered contraindicated in patients with heart failure and type 2 diabetes. And yet, we found that vulnerable patients exposed to metformin had lower mortality, less morbidity, and fewer hospitalizations than patients exposed to the much more commonly prescribed sulfonylureas. Conventional wisdom and practice guidelines have created a practice environment where all of the patients in our study who were taking metformin would be considered to be victims of "inappropriate" or "unsafe" prescribing. Whether our findings are sufficiently robust to either liberalize the careful use of metformin in diabetic

heart failure patients or simply engender sufficient equipoise to mandate a randomized trial is a question of clinical judgment. Although "patient safety" studies often seem to focus on finding and reducing the use of previously widely prescribed medications, which are of unproven benefit or even harm, our study should serve as a reminder that there is another side to the patient safety coin - some medications which are currently considered contraindicated may have been defined as such on the basis of little or no evidence beyond pathophysiologic rationale. Since this is considered insufficient evidence for efficacy, it should also be insufficient to declare harm. We believe that the onus in the patient safety literature should shift to acknowledge that both types of patient safety issues can lead to suboptimal prescribing practices.

Disclaimer

This study is based on non-identifiable data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

Table 2.1. Study Cohort Characteristics

Characteristic	Sulfonylurea Monotherapy (n = 773)	Metformin Monotherapy (n = 208)	Combination Therapy (n = 852)	P Value*
	No. (%) or Mean ± SD			
Age – yrs	74.8 ± 10.1	72.5 ± 10.6	70.0 ± 10.9	<0.001
Sex – male	451 (58)	123 (59)	472 (55)	0.40
Duration of Follow Up after diagnosis of heart failure (yrs)	2.3 ± 2.0	2.3 ± 1.8	2.8 ± 2.0	<0.001
Chronic Disease Score	10.7 ± 3.7	11.6 ± 3.6	11.7 ± 3.7	<0.001
Median	10.0	11.0	11.0	
Total Physician Visits†	41.6 ± 44.5	48.0 ± 40.0	52.3 ± 48.3	<0.001
Myocardial Infarction	72 (9)	20 (10)	91 (11)	0.645
Ischemic Heart Disease	152 (16)	32 (15)	130 (15)	0.874
Cerebrovascular Disease	88 (11)	19 (9)	84 (10)	0.490
Other Diseases of Arteries, Arterioles and Capillaries	27 (4)	6 (3)	29 (3)	0.91
Medications‡				
Thiazide Diuretics	214 (28)	59 (11)	263 (31)	0.36
Loop Diuretics	595 (77)	157 (76)	691 (81)	0.061
ACE Inhibitors	476 (62)	148 (71)	644 (76)	<0.001
ARBs	38 (5)	17 (8)	75 (9)	0.008
Antiplatelet Therapy	300 (39)	92 (44)	359 (42)	0.24
Antiarrhythmic Agent	369 (48)	109 (52)	423 (50)	0.45
Beta Blockers	251 (33)	90 (43)	369 (43)	<0.001
Spironolactone	113 (15)	29 (14)	114 (13)	0.77
Lipid Therapy	123 (16)	49 (24)	225 (26)	<0.001
Nitroglycerin	357 (46)	106 (51)	447 (53)	0.04

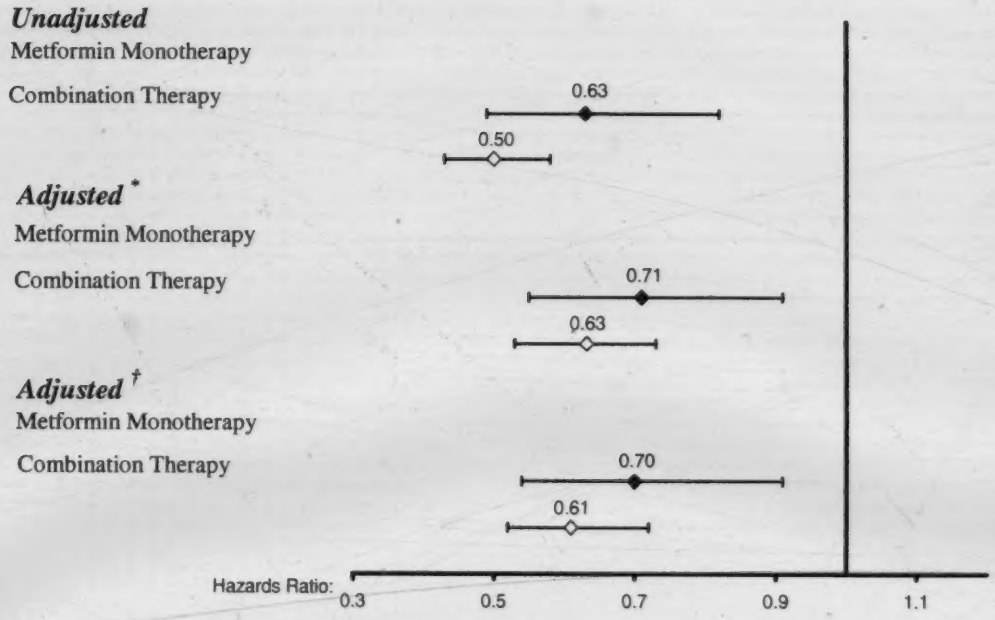
* omnibus p-values from χ^2 test or ANOVA; † total physician visits prior to HF diagnosis;‡categories not mutually exclusive

Table 2.2. Adjusted Hazard Ratios (95% CI) from Multivariate Cox Proportional Hazards Models

	All-Cause Mortality		All-Cause Hospitalization		Combined Endpoint	
	1 Year	Study End	1 Year	Study End	1 Year	Study End
Sulfonylurea Monotherapy*	1.0	1.0	1.0	1.0	1.0	1.0
Metformin Monotherapy	0.66 (0.44-0.97)	0.70 (0.54-0.91)	0.84 (0.67-1.04)	0.87 (0.73-1.05)	0.79 (0.65-0.98)	0.83 (0.70-0.99)
Combination Therapy	0.54 (0.42-0.70)	0.61 (0.52-0.72)	0.92 (0.80-1.06)	0.93 (0.83-1.05)	0.86 (0.75-0.98)	0.86 (0.77-0.96)

* Sulfonylurea monotherapy cohort is the reference group.

Figure 2.1. All-Cause Mortality at Study End According to Oral Antidiabetic Exposure

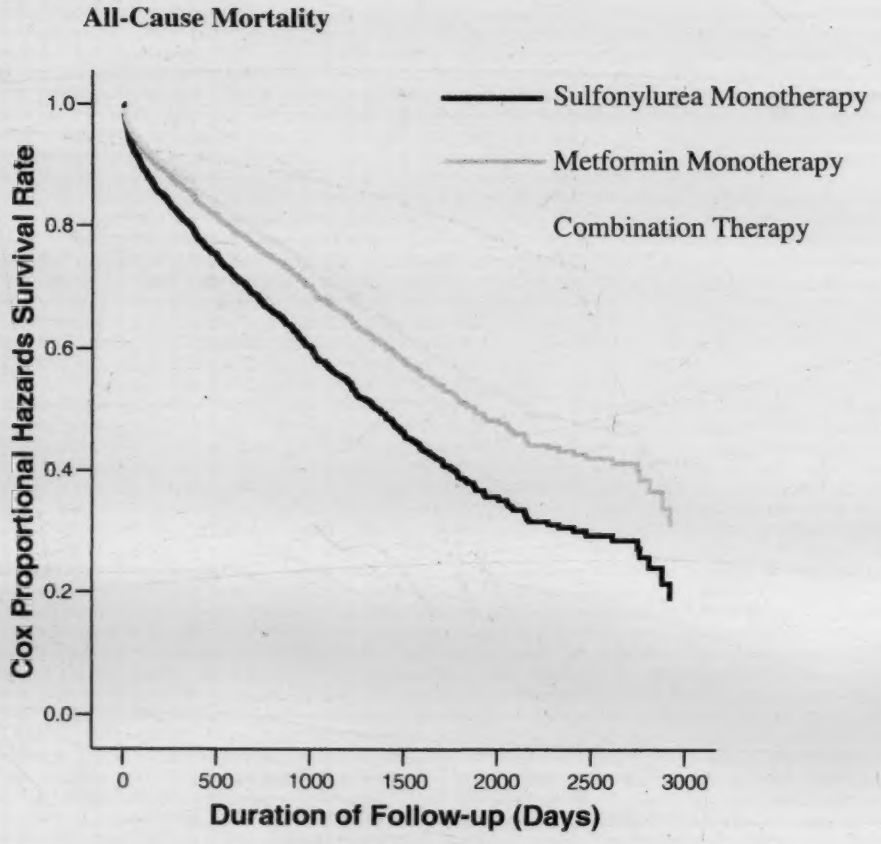


Note – Sulfonylurea monotherapy cohort is the reference group.

* Adjusted for age, sex, chronic disease score, drug therapies

† Adjusted for age, sex, chronic disease score, drug therapies, and total physician visits

Figure 2.2. Adjusted Kaplan-Meier Survival Curves at Study End in Patients with Heart Failure and Type 2 Diabetes, Stratified by Oral Antidiabetic Exposure



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CHAPTER 3: HOW SHOULD PATIENTS WITH DIABETES AND HEART FAILURE HAVE THEIR BLOOD SUGARS CONTROLLED? A SYSTEMATIC REVIEW OF THE EVIDENCE.

3.1 Abstract

Objective: To systematically review the literature on the relationship between antidiabetic therapies and morbidity and mortality in people with heart failure (HF) and diabetes.

Methods: Controlled studies (either randomized trials or cohort studies) evaluating antidiabetic agents and outcomes (death, hospitalizations) in patients with HF and diabetes were identified by searching various electronic databases, manually searching reference lists, and contact with investigators of included studies contacted. Two reviewers independently extracted data. Risk estimates for specific therapies were abstracted, and pooled estimates derived by meta-analysis where appropriate.

Results: Of 9,868 references initially identified, six studies (four cohort studies, two subgroup analyses of randomized trials) met the inclusion criteria. In four studies of 9,104 patients, use of insulin was associated with an increased risk for all-cause mortality in 3 studies and no effect in 1 study; OR 1.24 [1.03-1.51] and 3.42 [1.36-8.63] in the 2 studies without covariate adjustment, and HR 1.66 [95% CI 1.20-2.31] and 0.96 [0.88-1.05] in the 2 studies with multivariate analyses). In three studies of 3,327 patients, use of metformin was associated with a significant reduction in all-cause mortality in two studies; HR 0.86 [0.78-0.97] and 0.70 [0.54-0.91]), and a similar trend in the third HR 0.92, [0.72-1.18]. Metformin was not associated with increased all-cause or HF-specific hospitalizations in any studies. There were two studies of thiazolidinediones in 2,481 patients; one study demonstrated a significant reduction in all-cause mortality; HR 0.87 [0.80-0.94], and the other found no association. Thiazolidinediones were associated with an increased risk of HF-specific hospitalizations in both studies (pooled odds ratio 1.14 [1.04-1.25], I^2=0%, p=0.004). The 2 studies that specifically evaluated sulfonylureas (8,918 patients) had conflicting results, likely owing to differences in the comparator therapies rather than the effects of sulfonylurea alone. Important limitations were noted

in all of the studies, including lack of randomization, potential contamination of comparison groups, and confounding by indication.

Conclusion: Our systematic review indicates that metformin is the only antidiabetic agent that is not associated with harm in patients with HF and diabetes; and in fact, it was associated with reduced all-cause mortality in 2 of the 3 studies evaluating this outcome. Thus, labelling changes for metformin's current status as "contraindicated" should be strongly considered.

3.2 Introduction

Worldwide, over 171 million people have diabetes and the prevalence is expected to double by 2030.[1] Individuals with diabetes are at increased risk of developing heart failure[2,3] with the relative risk increasing by 10 to 15 percent per unit increase in A1c.[4-7] Conversely, heart failure is present in 25-40% of all adults with diabetes.[2,8-12] Moreover, diabetes portends poorer outcomes in people with heart failure[13-15] and it has been suggested that any level of hyperglycemia is associated with increased rates of hospitalization, even in patients without manifest diabetes.[16]

How best to achieve glycemic control in patients with diabetes and heart failure is therefore an important clinical question. Numerous antidiabetic therapies are now available to control hyperglycemia. However, their role in the management of diabetes in patients with heart failure is uncertain[17] and there is considerable controversy as to the overall impact of antidiabetic therapies on outcomes in people with comorbid diabetes and heart failure.[18,19] Even the optimal level of glucose control in patients with diabetes and heart failure remains uncertain and some evidence suggests that tight glycemic control (A1c $\leq$7%) may be associated with poorer survival compared to less tight control in patients with heart failure irrespective of the agent used.[20] As a result, it is possible that outcomes are affected not only by the choice of antidiabetic agent, but also by the degree of glycemic control achieved with the agent.

Given the paucity of evidence around these issues, current recommendations are based on pathophysiologic rationale, clinical experience, and expert consensus. A better understanding of the effects of antidiabetic agents on the health of people with heart failure and diabetes is needed.[17] Thus, we conducted a systematic review to examine the relationship between antidiabetic therapies and outcomes in people with heart failure and diabetes.

3.3 Methods

A comprehensive search strategy was used to search various electronic databases (Medline (1966-2006), HealthSTAR (1966-2006), EMBASE (1980-2006), Cumulative Index to Nursing and Allied Health Literature (1982-2007), International Pharmaceutical Abstracts (1970-2007), Allied and Complementary Medicine (1985-2007), Cochrane

Central Register of Controlled Trials (1991-2007), and the Web of Science (1900-2007) from their date of inception until the week of February 28, 2007 for studies with contemporaneous comparison groups (e.g., randomized controlled trials or cohort studies) that evaluated the association between antidiabetic therapies and clinical outcomes of hospitalizations and/or mortality in patients with diabetes and heart failure (Appendix A). In addition, articles were also retrieved by manually searching reference lists from original studies and review articles, and contact with experts and authors of included studies. The search applied no language restrictions. The risk of developing heart failure associated with antidiabetic therapies was not assessed.

Relevant citations were identified by 2 reviewers (DTE and DFB) independently and included in the review if they met the following criteria: described original research, included subjects with both diabetes and heart failure, evaluated the effects of antidiabetic therapies on health outcomes (i.e., mortality, all-cause hospitalization, and heart failure specific hospitalizations), and included a contemporaneous control group for comparison. Any discrepancies were resolved by consensus after review by a third investigator (JAJ). All data were extracted and the methodological quality of included studies was assessed using a previously validated quality checklist[21] by DTE and DFB independently. The maximum score on the quality checklist is 32 with a score of 12 (38%) or greater considered to be acceptable quality.[21,22]

Analysis

To summarize the effects of antidiabetic therapies on outcomes of interest (i.e., all-cause mortality or hospitalizations), we abstracted the risk estimates and 95% confidence intervals from each study. If appropriate, we then pooled data across studies using Random Effects models if there was not excessive statistical heterogeneity (measured using the I^2 statistic and defined *a-priori* as $P \leq 0.10$ or $I^2 \geq 50\%$).[23] All analyses were conducted using Cochrane Review Manager 4.2 (Cochrane Collaboration, Oxford, United Kingdom).

3.4 Results

Our search yielded 9,868 citations, and 6 studies met our the inclusion criteria – 3 retrospective cohort studies, 2 retrospective subgroup analyses from randomized trials, and 1 prospective cohort study (Figure 3.1).[18,19,24-27] Interobserver agreement was k=0.75 for study inclusion.

Of the 6 studies, 3 studies had more than 2 comparison groups. As a result, 4 studies evaluated the effect of insulin therapy in patients with heart failure (n=9,104), 3 studies examined metformin (n=3,327), 2 studies evaluated thiazolidinediones (TZD) (n=2,481), and sulfonylurea therapy was compared against other agents in 2 studies (n=8,918) studies. No studies specifically evaluated the effects of alpha-glucosidase inhibitors (e.g., acarbose, meglitol) or nonsulfonylurea insulin secretagogoues (e.g., repaglinide, nateglinide) in patients with heart failure and we did not identify any randomized trials that directly addressed our question. The population studied, study design, statistical analysis, outcomes, limitations, and key findings for the 6 included studies can be found in Table 3.1 (characteristics) and Table 3.2 (results). Overall, the 6 included studies were of acceptable quality, with a methodological quality score ranging from 13 (41%) to 18 (56%) (Table 3.1); the median quality score was 16 (50%).

Table 3.3 provides a summary of the statistical heterogeneity and quantification using the I^2 statistic. Due to significant statistical heterogeneity, a formal meta-analysis was not performed for the effects of insulin, metformin, or thiazolidinediones on all-cause mortality. With respect to hospitalizations, the meta-analyses were only interpretable for the effects of metformin therapy on all-cause hospitalization and thiazolidinedione therapy on heart failure-related hospitalization (Table 3.3).

Summary of studies

Insulin

Outcomes with insulin were evaluated in a subgroup analysis of 496 patients with diabetes and left ventricular dysfunction (ejection fraction <40% after acute myocardial infarction) from the Survival and Ventricular Enlargement (SAVE) Trial (Table 3.1).[27] After multivariate adjustment, compared to 328 non-insulin treated patients (diet, sulfonylurea, or metformin therapy), the 168 insulin-treated patients had significantly

increased risk of all-cause mortality; adjusted HR (aHR) 1.66 [95% CI 1.20-2.31]), and cardiovascular morbidity (i.e., hospitalization for heart failure or prescription of an open label angiotensin converting enzyme inhibitor, or myocardial infarction) and mortality; aHR 1.38 [95% CI 1.06-1.80]) (Table 3.2).

The impact of insulin therapy was also evaluated in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study (Table 3.1).[24] Although insulin therapy was only compared to patients without diabetes in adjusted analyses, unadjusted risk ratios calculated from the raw data presented in the paper suggest that insulin therapy is associated with an increased risk of all-cause mortality; risk ratio 1.25 [95% CI 1.03-1.51] and cardiovascular death or heart failure hospitalization; risk ratio 1.55 [95% CI 1.29-1.86] compared to non-insulin therapy in diabetic subjects (Table 3.2).[24,28]

Outcomes with insulin were also assessed by Smooke *et al.* in 554 consecutive patients referred to a university medical centre for heart failure management (Table 3.1).[25] Of these patients, 132 (24%) patients had a diagnosis of diabetes and were prospectively followed for 11.7 months. Although direct comparison of insulin therapy to non-insulin therapy was not completed in diabetic subjects, extrapolation from the raw data in the paper suggests an unadjusted risk ratio for all-cause mortality of 3.42 [95% CI 1.36-8.64] at 1 year and 2.20 [95% CI 0.95-5.08] at two years (Table 3.2) for diabetics treated with insulin compared to diabetics treated without insulin.

Masoudi *et al.* also evaluated the effects of insulin on mortality in a retrospective cohort study of 16,417 Medicaid beneficiaries with diabetes who were discharged after hospitalization with a primary diagnosis of heart failure (Table 3.1).[18] Unlike previous studies, no association between the use of insulin therapy and mortality was observed; aHR 0.96 [95% CI 0.88-1.05] compared to patients receiving metformin, TZDS, sulfonylureas, nonsulfonylurea insulin secretagogues, or alpha-glycosidase inhibitors.[18]

Oral Antidiabetic Agents

Metformin

Outcomes with metformin were evaluated by Inzucchi *et al.* in a retrospective cohort study of Medicare beneficiaries with diabetes discharged after hospitalization with

an acute myocardial infarction (Table 3.1).[26] Subgroup analysis of the subjects with diabetes and moderate to severe impaired left ventricular systolic function (n=2,875) suggested that after multivariate adjustment metformin therapy was not associated with any risk of all-cause mortality at 1 year compared to patients receiving other agents (i.e., sulfonylureas, non-sulfonylurea insulin secretagogues, alpha-glucosidase inhibitors, or insulin), (n=406); aHR 0.92 [95% CI 0.72-1.18] (Table 3.2).[26]

In their study of Medicaid beneficiaries with diabetes who were discharged after hospitalization with a primary diagnosis of heart failure mentioned earlier, Masoudi *et al.* also evaluated the effect of metformin on all-cause mortality at 1 year (Table 3.1).[18] After multivariate adjustment, compared to patients not receiving insulin sensitizers (i.e., receiving sulfonylureas, non-sulfonylurea insulin secretagogues, alpha-glucosidase inhibitors, or insulin) (n=12,069), all-cause mortality was significantly lower for patients treated with metformin (n=1861); aHR 0.86 [95% CI 0.78-0.97], as well as in patients treated both with metformin and TZDs (n=261); aHR 0.76 [95% CI 0.58-0.99] (Table 3.2). Additionally, Masoudi *et al.* found no difference in the risk for all-cause hospital readmissions for patients receiving metformin; aHR 0.94 [95% CI 0.89-1.01] and a lower risk in patients treated with both metformin and TZDs; aHR 0.82 [95% CI 0.69-0.96] (Table 3.2). A lower risk was also observed for metformin users with respect to heart failure related readmissions; aHR 0.92 [95% CI 0.86-0.99] and a trend towards reduction in patients receiving both metformin and TZDs; aHR 0.85 [95% CI 0.71-1.01].

In a retrospective analysis using administrative records, Eurich *et al.* compared metformin alone, or in combination with sulfonylurea therapy, to sulfonylurea monotherapy in 1,833 patients with newly treated diabetes and incident heart failure (Table 3.1).[19] After multivariate adjustment, all-cause mortality was significantly lower with metformin monotherapy; aHR 0.66 [95 % CI 0.44-0.97] at one year and aHR 0.70 [95% CI 0.54-0.91] after 2.5 years, or with combination metformin-sulfonylurea therapy; aHR 0.54 [95% CI 0.42-0.70] at one year and aHR 0.61 [95% CI 0.52-0.72] after 2.5 years (Table 3.2). A reduction in the composite outcome of all-cause mortality or hospitalization was also observed at the end of follow-up for metformin monotherapy group; aHR 0.83 [95% CI 0.70-0.99] and for combination therapy; aHR 0.86 [95% CI 0.77-0.96] (Table 3.2).

For the two studies which assessed the effect of metformin on all-cause hospitalization at 1 year[18,19], the pooled effect suggests that metformin therapy may be associated with reduced all-cause hospitalizations at 1 year compared to non-metformin therapies; pooled odds ratio 0.85 [95% CI 0.76-0.95], I^2=20.9%, p=0.004 (Figure 3.2).

Thiazolidinediones

Outcomes with thiazolidinediones (TZDs) were also evaluated in the Inzucchi *et al.* study (Table 3.1). After multivariate adjustment, TZDs (n=255) were associated with an increased risk of all-cause mortality at 1 year compared to patients not receiving insulin sensitizers (i.e., receiving sulfonylureas, nonsulfonylurea insulin secretagogues, alpha-glucosidase inhibitors, or insulin); aHR 1.04 [95% CI 0.83-1.31] (Table 3.2). There was also a trend towards an increased risk of heart failure related readmissions associated with TZDs; aHR 1.15 [95% CI 0.97-1.38].

In the second study, Masoudi *et al.* also evaluated the effect of TZDs on all-cause mortality at 1 year (Table 3.1).[18] After multivariate adjustment, compared to patients not receiving insulin sensitizers (i.e., receiving sulfonylureas, nonsulfonylurea insulin secretagogues, alpha-glucosidase inhibitors, or insulin) (n=12,069), all-cause mortality at 1 year was significantly lower for patients treated with TZDs (n=2,226); aHR 0.87 [95% CI 0.80-0.94] (Table 3.2). Additionally, Masoudi *et al.* found no difference in the risk for all-cause hospital readmissions for patients receiving TZDs; aHR 1.04 [95% CI 0.99-1.10]. However, a small increased risk of heart failure related readmissions was observed for patients receiving TZDs; aHR 1.06 [95% CI, 1.00-1.12].

In the two studies which evaluated heart failure related hospitalizations at 1 year[18,26], the pooled effect suggests that TZDs may be associated with an increased risk of heart failure related hospitalizations at 1 year compared to non-TZD therapies; pooled odds ratio 1.14 [95% CI 1.04-1.25], I^2=0%; p=0.004 (Figure 3.3).

Sulfonylureas

Few studies formally evaluated sulfonylurea therapy as an independent exposure group. It is important to consider, however, that in the studies evaluating other oral therapies, sulfonylurea therapy was used in approximately 50% of all patients comprising

the main comparator groups (n~8000). As a result, sulfonylurea therapy was well represented in all of the studies evaluating oral antidiabetic therapies included in our review.

In addition to the results observed with sulfonylurea therapy relative to metformin use from Eurich *et al*,[19] the only other evaluation of outcomes with sulfonylurea exposure was conducted by Masoudi *et al*.[18] After multivariate analysis, no increased risk of mortality at 1 year was observed for patients receiving sulfonylurea therapy compared to patients receiving non-sulfonylurea insulin secretagogues, alpha-glucosidase inhibitors, or insulin; aHR 0.99 [95% CI 0.91-1.08].

3.5 Discussion

Heart failure is a common comorbidity in patients with diabetes. Despite the significant morbidity and mortality associated with the disease, our systematic review found few studies that have formally compared antidiabetic therapies in this important population. Although several studies have evaluated the incidence of heart failure associated with the use of various antidiabetic therapies,[3,8,29-32] our review focused solely on the impact of antidiabetic therapies in people with comorbid heart failure and diabetes. Of the six studies included in this review, all studies were observational and there was no randomized controlled trial evidence to address our question. All studies were published in the past 2 years, and focused on use of insulin, TZDs, or metformin therapy.

In the four studies that specifically evaluated the use of insulin therapy, three suggested an increase in mortality, and one reported no association with mortality, although statistical heterogeneity precluded formal meta-analysis. Importantly, in two of the studies reporting an increased mortality, there was no multivariate adjustment for the comparison of insulin therapy to non-insulin therapy in patients with diabetes. Furthermore, none of the studies randomized patients to insulin or non-insulin treatment. As a result, it is difficult to discern if this truly represents an adverse insulin effect or is simply confounding by indication. It is quite probable, that the use of insulin therapy in these studies may have been a marker for more advanced diabetes and/or vascular disease.[27] As a result, insulin therapy may not, in itself, be associated with an increase in adverse effects in this population. Indeed, in the Masoudi *et al*. study, which had

extensive adjustment for clinically important variables and compared insulin with other antidiabetic therapies, insulin therapy was not associated with an increased risk of mortality.[18]

According to current labeling, metformin therapy is absolutely contraindicated in patients with heart failure requiring pharmacological treatment due to concerns over the development of lactic acidosis. However, our analysis revealed that metformin therapy may be associated with lower mortality rates, although statistical heterogeneity precluded formal meta-analysis. Furthermore, no study observed an increase in adverse events with metformin therapy and both studies which evaluated all-cause hospitalizations in metformin users reported results suggesting that metformin use is associated with a lower rate of all-cause hospitalizations than use of other antidiabetic therapies.

Thiazolidinediones are also relatively contraindicated in patients with New York Heart Association Class III or IV due to concerns of fluid retention which may worsen heart failure symptoms.[33] Yet, our analysis revealed that TZDs may be associated with lower mortality rates, although statistical heterogeneity precluded formal meta-analysis. In both the Inzucchi *et al.* and Masoudi *et al.* studies, however, there was a trend towards increasing heart failure related readmissions for patients receiving TZDs[18,26], a risk which was affirmed with formal pooling of the data. This is consistent with randomized controlled trial evidence, including the recently published interim analysis of the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) study, which have consistently shown increased fluid retention and heart failure admissions with the use of TZDs in patients without pre-existing HF.[32,34-36] Furthermore, given the recent controversy with respect to the use of thiazolidinediones and the increased risk of myocardial infarction[37], the overall impact on health remains uncertain.[38]

Although the lower mortality rates associated with use of metformin or TZDs are consistent with those observed in randomized controlled trials of insulin sensitizers in other diabetes populations[32,34,39], it is important to consider that none of the 3 included studies were randomized controlled trials. Although a wide range of demographic and patient characteristics were adjusted for in the studies, it is possible that differences may have existed between the study groups with respect to severity of diabetes, heart failure,

or other cardiovascular risk factors. Specifically, the commonly perceived risks of insulin sensitizer therapy may have resulted in the preferential use of these drugs in patients who were perceived to be at lower risk than those patients in whom other therapies were used. Furthermore, it is important to recognize that of the 3 studies, Eurich *et al.* was the only study to specifically evaluate the effects of oral antidiabetic therapy used as monotherapy. As a result, potential contamination of comparison groups due to the use of multiple antidiabetic therapies is possible in the Inzucchi *et al.* and Masoudi *et al.* studies.

Although sulfonylurea therapy was included in all of the studies evaluated, only Eurich *et al.* and Masoudi *et al.* specifically evaluated sulfonylureas as a independent exposure.[18,19] Although results from Eurich *et al.* suggest sulfonylurea monotherapy may be associated with worse outcomes, this was not observed in the Masoudi *et al.* study.[18,19] The discrepancy may be due, in part, to the comparator group used in the studies. In Eurich *et al.*, sulfonylurea monotherapy was compared to metformin therapy, which has been shown to be beneficial in all similar studies, while Masoudi *et al.* compared sulfonylurea exposure (alone or in combination) to therapies which did not specifically include metformin. As a result, in the Eurich *et al.* study, it is not possible to determine if the observed risk estimates were due to an adverse effect of sulfonylurea therapy, a beneficial effect of metformin therapy, or confounding by indication. Although these results are consistent with other studies evaluating sulfonylurea therapy [39-42], a recent meta-analysis has suggested that sulfonylurea therapy is not associated with an increase in cardiovascular events.[43] Given the current controversy surrounding the use of sulfonylurea therapy in patients with pre-existing cardiovascular disease[44], more research is need to determine the true impact of sulfonylurea therapy in people with diabetes and heart failure.

The results of our systematic review must be viewed in light of its limitations. Inherent to any systematic review is the potential for publication bias. Studies that may have evaluated the use of antidiabetic agents in heart failure patients as part of a stratified or secondary analysis may not have been easily identified using standard search strategies. However, manual searches and contact with primary authors of the included studies did not provide any additional articles. It is therefore unlikely that any relevant

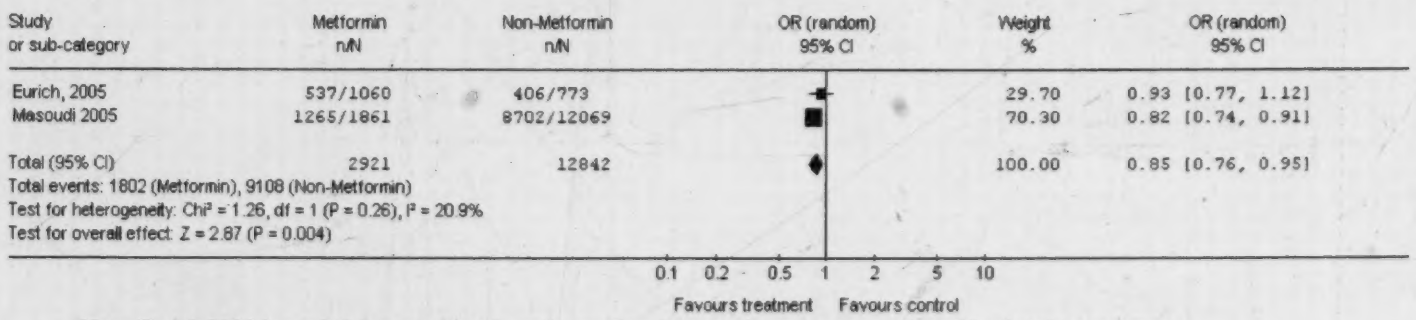
articles were missed. Second, as previously mentioned, the studies included in this review were all observational in nature and none randomized patients to different antidiabetic therapies. As a result, the effects of unmeasured confounding variables could not be fully explored and may be a limitation of all of the reported studies.

The results of our systematic review suggest that of the current antidiabetic therapies, metformin is the only agent not associated with any measurable harm in people with diabetes and heart failure and, in fact, has been associated with reduced mortality. Given the large number of people affected with diabetes and heart failure and the fact that this population is expected to rapidly increase, evidence on how to optimally control glycemic levels in this population is urgently needed. It is therefore imperative that research be undertaken to determine the optimal approach for glycemic control in patients with heart failure. Ideally, this research should be a randomized controlled trial which includes the use of metformin or thiazolidinedione therapy in patients with heart failure and diabetes. Furthermore, this trial should be aimed at evaluating the impact of these therapies on glycemic control and its relation to long term outcomes, as well as, the impact of these therapies on morbidity and mortality in people with heart failure and diabetes. Until these trial data become available, we believe our results, at the least, suggest that the "contraindicated" labelling for metformin in patients with heart failure needs to be revisited.[19,45,46]

Figure 3.1. QUOROM Diagram of Systematic Search

Data Sources:
Medline (1966-2006) HealthSTAR (1966-2006) EMBASE (1980-2006) Cumulative Index to Nursing and Allied Health Literature (1982-2007) International Pharmaceutical Abstracts (1970-2007) Allied and Complementary Medicine (1985-2007) Cochrane Central Register of Controlled Trials (1991-2007) Web of Science (1900-2007)
Identified 9868 Citations:
Reviewed 9868 titles and Abstracts: First Round • 2481 excluded – duplicates • 665 excluded – not diabetes • 701 excluded – not heart failure • 829 excluded – non-human studies or cellular studies • 830 excluded – reviews, guidelines, letters, editorials • 4190 excluded – not relevant to research question
Reviewed 172 titles and Abstracts: Second Round • 3 excluded – not diabetes • 8 excluded – case report • 8 excluded – no relevant outcome measure • 10 excluded – not heart failure • 15 excluded – no antidiabetic agents assessed • 17 excluded – reviews, guidelines, letters, editorials • 38 excluded – not relevant to research question
Reviewed 73 complete articles and reference lists: • 2 excluded – no comparator group • 4 excluded – case report • 26 excluded – no relevant outcome measure • 19 excluded – not heart failure • 7 exclude – not diabetes • 5 excluded – no antidiabetic agents assessed • 4 excluded – reviews, guidelines, letters, editorials
6 articles included for review

Figure 3.2: Pooled Odds Ratio for Metformin Compared to Non-Metformin Therapy on All-Cause Hospitalization at 1 Year


Study
or sub-category
Metformin
n/N
Non-Metformin
n/N
OR (random)
95% CI
Weight
%
OR (random)
95% CI
Eurich, 2005 537/1060 406/773 29.70 0.93 [0.77, 1.12]
Masoudi 2005 1265/1861 8702/12069 70.30 0.82 [0.74, 0.91]
Total (95% CI) 2921 12842 100.00 0.85 [0.76, 0.95]
Total events: 1802 (Metformin), 9108 (Non-Metformin)
Test for heterogeneity: Chi² = 1.26, df = 1 (P = 0.26), I² = 20.9%
Test for overall effect: Z = 2.87 (P = 0.004)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Note: Eurich 2005 is pooled data resulting from the metformin monotherapy group and combination therapy group (pooled test for heterogeneity p=0.70; I^2=0%)

Figure 3.3: Pooled Odds Ratio for TZDs Compared to Non-TZD Therapy on Heart Failure Related Hospitalization at 1 Year

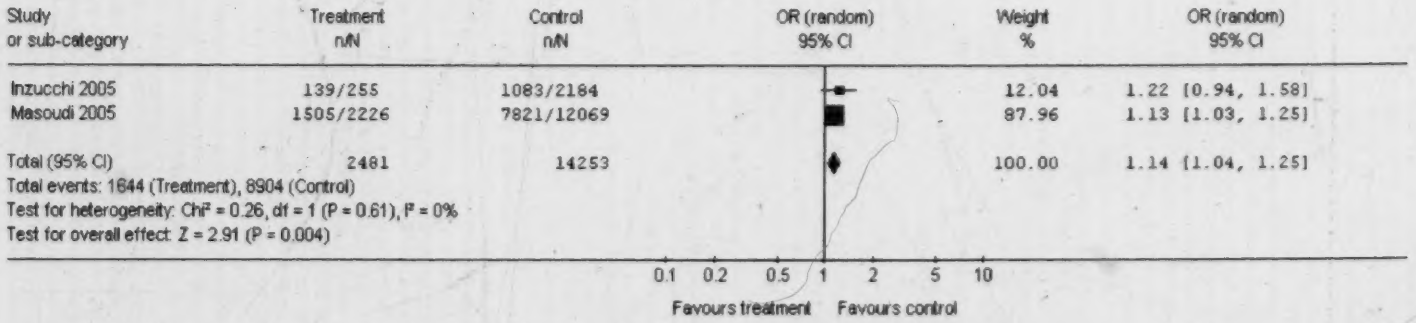

Study
or sub-category
Treatment
n/N
Control
n/N
OR (random)
95% CI
Weight
%
OR (random)
95% CI
Inzucchi 2005 139/255 1083/2184 12.04 1.22 [0.94, 1.58]
Masoudi 2005 1505/2226 7821/12069 87.96 1.13 [1.03, 1.25]
Total (95% CI) 2481 14253 100.00 1.14 [1.04, 1.25]
Total events: 1644 (Treatment), 8904 (Control)
Test for heterogeneity: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%
Test for overall effect: Z = 2.91 (P = 0.004)
0.1 0.2 0.5 1 2 5 10
Favours treatment
Favours control

Table 3.1. Methods, Design, and Quality of Studies for Antidiabetic Agents in the Treatment of Diabetes with Heart Failure

Study (Agents)	Design (n)	Inclusion Criteria	Exclusion Criteria	Agents Evaluated	Method of Analysis	Covariates Included in Analysis	Duration	Methodologic quality checklist score[‡]
Murcia et al. 2004[27]	Retrospective subgroup analysis of RCT SAVE (n=496)	Diabetes, ≥21 but <80 years, LVEF ≤40% after MI	Contraindication to ACE inhibitors or need for therapy to treat HF or hypertension, Cr>221 mmol/L; unstable illness; active ischemia	1. Insulin	Multivariate Cox proportional hazards regression	age, sex, LVEF, previous MI, killip class ≥ II, thrombolytic therapy, beta-blocker use, and captopril assignment	Mean 3.5 years	44%
Pocock et al.2006[24]	Retrospective subgroup analysis of RCT CHARM (n=2160)*	≥18 years, symptomatic HF (NYHA Class II-IV) of at least 4 weeks duration	Cr ≥ 265 umol/L, K^+ >5.5 mmol/L, bilateral renal stenosis, symptomatic hypotension, women of childbearing potential not receiving contraceptives, critical aortic or mitral stenosis, MI, stroke or open heart surgery in the previous 4 weeks, use of ARBs in previous 2 weeks, any non-cardiac disease likely to limit survival to 2 years	1. Insulin	Univariate	No covariate adjustment	Median 37.7 months	41%

Table 3.1. Continued...

Study (locale)	Design (n)	Inclusion Criteria	Exclusion Criteria	Agents Evaluated	Method of Analysis	Covariates Included in Analysis	Duration	Methodologic quality checklist score
Smooke et al. 2005 [25]	Prospective cohort study (n=132)†	Consecutive patients with HF referred to specialty clinic for HF management and/or transplant evaluation for systolic dysfunction HF (LVEF<40%) from January 1, 2000 to January 30, 2003	No exclusions reported	1. Insulin	Univariate	No covariate adjustment	Mean 11.7 months	63%
Masoudi et al. 2006	Retrospective cohort study (n=16,417)	Patients with diabetes receiving antidiabetic agents upon discharge with a principle discharge diagnosis of HF	<65 years of age, died during hospitalization, unknown date of death, unknown readmission data, discharge to a hospice, no pharmacological treatment for diabetes at discharge	1. Insulin 2. Metformin 3. TZDs 4. SU	Stepwise multivariate Cox proportional hazards regression	Demographics (Age, sex, race); cardiac history (history of MI, hypertension, CAD, PTCA; non-CV history (admission source, mobility, cerebral vascular accident, chronic pulmonary disease, urinary incontinence, dementia) clinical characteristics at admission (systolic blood pressure, respiratory rate, HF, Na^+, glucose, BUN, Cr, WBC count, hematocrit); hospital course (AF, HF pulmonary edema on admission, cardiac catheterization, PTCA, CABG, diabetes complications); discharge prescriptions; diabetes severity; sampling frame.	Not reported	50%

Table 3.1. Continued...

Study (locale)	Design (n)	Inclusion Criteria	Exclusion Criteria	Agents Evaluated	Method of Analysis	Covariates Included in Analysis	Duration	Methodologic quality checklist score
Inzucchi et al., 2005[26]	Retrospective cohort study (n=2,875)‡	Patients with diabetes receiving antidiabetic agents upon discharge from hospital for a MI	Unconfirmed MI, long term hemodialysis, <65 years of age, died during hospitalization, unknown date of death, unknown readmission data, discharge to a hospice, transferred to another hospital, left against medical advice, no pharmacological treatment for diabetes at discharge	1. Metformin 2. TZDs	Stepwise multivariate Cox proportional hazards regression	Potential covariates included demographics (Age, sex, race); cardiac history (history of HF, MI, hypertension, revascularization; non-CV history (admission source, mobility, cerebral vascular accident, chronic pulmonary disease, urinary incontinence, dementia) clinical characteristics at admission (systolic blood pressure, respiratory rate, HF, Na^+, glucose, BUN, Cr, WBC count, hematocrit); hospital course (AF, HF/pulmonary edema on admission, cardiac catheterization, PTCA, CABG, diabetes complications); discharge prescriptions; diabetes severity; sampling time frame; patient clustering by hospital	Not reported	47%

Table 3.1. Continued…

Study (locale)	Design (n)	Inclusion Criteria	Exclusion Criteria	Agents Evaluated	Method of Analysis	Covariates Included in Analysis	Duration	Methodologic quality checklist score
Eurich et al. 2005[19]	Retrospective cohort study (n=1,833)	New users of oral antidiabetic agents with incident onset HF	Insulin use, prevalent HF (diagnosis of HF prior before starting oral antidiabetic agents)	1. Metformin 2. SU	Multivariate Cox proportional hazards regression	Age, sex, modified chronic disease score, prescription medications affecting outcomes in people with diabetes and/or HF, total physician visits prior to HF diagnosis, propensity score (not included in final models)	Mean 2.5 years	50%

- RCT-Randomized Controlled Trial; MI – Myocardial infarction; NYHA – New York Heart Association; HF – Heart Failure; LVEF - Left ventricular Ejection Function; TZD – thiazolidinediones;; SAVE- Survival and Ventricular Enlargement; CHARM-Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; Cr – Creatinine; BUN – Blood Urea Nitrogen; WBC – White Blood Cell Count; CAD – Coronary Artery Disease; PTCA – Percutaneous Transluminal Coronary Angioplasty; CABG – Coronary Artery Bypass Graft; AF – Atrial Fibrillation

* - 7599 total subjects included in study. Analysis was restricted to 2160 subjects with diabetes

† - 575 total subjects included in study; Analysis restricted to 132 subjects with diabetes

‡ - 8.872 subjects included in study. Analysis restricted to 2876 subjects with left ventricular systolic dysfunction

§ - Methodological checklist score as presented by Down and Black for the assessment of the methodological quality of randomized and nonrandomized studies of health interventions. Scored out of a maximum of 32 points and displayed as a percentage.[21,22]

Table 3.2. Results of studies assessing antidiabetic agents in the treatment of diabetes in patients with heart failure

Study	Study Agent (n)	Comparator (n)	Outcome	Unadjusted Risk Estimate (95% CI)	Adjusted Risk Estimate (95% CI)	Potential limitations and threats to validity*	Key findings and conclusion
Murcia et al., 2004[27]	Insulin therapy (n=168)	Non-insulin therapy (metformin, sulfonylurea, diet)(n=328)	1. All-Cause Mortality 2. CV morbidity and mortality	1.96 (1.33-1.90) 1.96 (1.33-1.90)	HR 1.66 (1.20-2.31) HR 1.38 (1.06-1.80)	1. selection bias (data derived from RCT in post MI patients) 2. uncertain drug exposure (drug use defined at start of trial, exposure to drug throughout follow-up uncertain) 3. confounding by severity of diabetes (no data on glucose control, duration of diabetes) 4. limited adjustment for clinical data 5. no data on type of oral antidiabetic agents used	Patients with diabetes who survive a MI with LV dysfunction are at increased risk of subsequent mortality or cardiovascular events. Insulin therapy is associated with an even higher risk compared to non-insulin treated diabetes.
Pocock et al., 2006 [24]	Insulin therapy (n=706)	Non-insulin (diet, sulfonylurea, metformin, TZDs) (n=1,454)	1. All-cause mortality 2. CV mortality or HF hospitalization	1.24 (1.03-1.51) 1.55 (1.29-1.86)	No adjusted estimate No adjusted estimate	1. confounding by severity of diabetes (no data on glucose control, duration of diabetes) 2. no data on type of oral antidiabetic agents used 3. Uncertain exposure (criteria used to define 'insulin use' not stated; no data on duration of drug use; exposure to drug throughout follow-up uncertain) 4. selection bias (data derived from RCT) 5. no adjusted results comparing insulin to non-insulin therapies in patients with diabetes	In patients with systolic dysfunction and preserved systolic function, the presence of diabetes and diabetes treated with insulin therapy highly prognostic of all cause mortality, CV death, or HF hospitalization.

Table 3.2. Continued...

Study	Study Agent (n)	Comparator (n)	Outcome	Unadjusted Risk Estimate (95% CI)	Adjusted Risk Estimate (95% CI)	Potential limitations and threats to validity*	Key findings and conclusion
Smooke et al., 2005 [25]	Insulin therapy (n=43)	Non-insulin (diet, sulfonylurea, metformin, TZDs) (n=89)	1. All-cause mortality at 1 year 2. All-cause mortality at 2 years	3.42 (1.36-8.63) 2.20 (0.95-5.08)	No adjusted estimate No adjusted estimate	1. selection bias (advanced heart failure patients only) 2. small sample size initially and 15% lost to follow-up (few patients left to evaluate for 2 yr outcome). 3. uncertain exposure (no data on duration of drug use; exposure to drug throughout follow-up uncertain) 4. significant baseline differences (incomplete adjustment possible due to small sample size) 5. no adjusted results comparing insulin to non-insulin therapies in patients with diabetes 6. short duration of follow-up (mean 11.7 months)	Insulin treated diabetes is associated with a marked increase in mortality. No increased risk of mortality for non-insulin diabetes
Masoudi et al., 2005[18]	Insulin (n=8,187)	SU, NonSU secreatogoues, alpha-glucosidase inhibitors, metformin, thiazolidinediones (n=8,230)	1. All-cause mortality at 1 year	No absolute values reported	HR 0.96 (0.88-1.05)	1. selection bias (>65 years only) 2. uncertain exposure (cohort created based on discharge medications; exposure to drug throughout follow-up uncertain) 3. short duration of follow-up (1 yr outcomes)	Insulin therapy not associated with an increase risk of mortality.

Table 3.2. Continued...

Study	Study Agent (n)	Comparator (n)	Outcome	Unadjusted Risk Estimate (95% CI)	Adjusted Risk Estimate (95% CI)	Potential limitations and threats to validity*	Key findings and conclusion
Inzucchi et al., 2005[26]	Metformin (n=406)	No-insulin sensitizer (SU, nonSU secreatogoues, alpha-glucosidase inhibitors, insulin) (n=2,184)	1. All-cause mortality at 1 year	No absolute values reported	HR 0.92 (0.72-1.18)	1. selection bias (>65 years post MI only) 2. small sample size (few subjects in LV dysfunction subgroup) 3. uncertain exposure (cohort created based on discharge medications; exposure to drug throughout follow-up uncertain) 4. short duration of follow-up (1 yr outcomes) 5. No absolute values reported	In the subgroup of patients with LV dysfunction, metformin did not increase the risk of mortality.
Masoudi et al., 2005[18]	Metformin (n=1,861)	No-insulin sensitizer (SU, nonSU secreatogoues, alpha-glucosidase inhibitors, insulin) (n=12,069)	1. All-cause mortality at 1 year 2. All-cause hospitalization at 1 year 3. HF readmission at 1 year	0.58 (0.52-0.65) 0.82 (0.74-0.91) 0.52 (0.57-0.48)	HR 0.86 (0.78-0.97) HR 0.94 (0.89-1.01) HR 0.92 (0.86-0.99)	1. selection bias (>65 years only) 2. uncertain exposure (cohort created based on discharge medications; exposure to drug throughout follow-up uncertain) 3. short duration of follow-up (1 yr outcomes)	Metformin therapy associated with substantial reduction in mortality, all-cause hospitalization, and HF related hospitalizations. Metformin therapy did not increase the risk for a hospitalization due to lactic acidosis

Table 3.2. Continued...

Study	Study Agent (n)	Comparator (n)	Outcome	Unadjusted Risk Estimate (95% CI)	Adjusted Risk Estimate (95% CI)	Potential limitations and threats to validity*	Key findings and conclusion
Eurich et al. 2005[19]	Metformin monotherapy (n=208)	SU monotherapy (n=773)	1. All-cause mortality at 1 year	0.43 (0.29-0.65)	HR 0.66 (0.44-0.97)	1. Selection bias (uncertain diagnostic accuracy of HF in physician service file; insulin users excluded)	Metformin therapy associated with substantial reductions in all-cause mortality and a trend towards reduced risk of all-cause hospitalization.
			2. All-cause mortality at study end	0.40 (0.29-0.56)	HR 0.70 (0.54-0.91)	2. uncertain exposure (cohort created based on a single prescription for antidiabetic medications; exposure to drug throughout follow-up uncertain; combination therapy not necessarily concurrent therapy)	
			2. All-cause hospitalization at 1 year	0.87 (0.64-1.18)	HR 0.84 (0.67-1.04)		
			3.All-cause hospitalization at study end	0.96 (0.69-1.34)	HR 0.87 (0.73-1.05)	3. Confounding by severity of diabetes or heart failure (no clinical data or functional status)	
			3. Combined all-cause mortality or hospitalization at 1 year	0.76 (0.55-1.03)	HR 0.79 (0.65-0.98)	4. Small sample size (only 208 in metformin monotherapy cohort)	
			4. Combined all-cause mortality or hospitalization at study end	0.58 (0.40-0.85)	HR 0.83 (0.70-0.99)		

Table 3.2. Continued...

Study	Study Agent (n)	Comparator (n)	Outcome	Unadjusted Risk Estimate (95% CI)	Adjusted Risk Estimate (95% CI)	Potential limitations and threats to validity	Key findings and conclusion
Eurich et al. 2005[19]	Metformin and SU combination therapy (n=852)	SU monotherapy (n=773)	1. All-cause mortality at 1 year	0.34 (0.26-0.44)	HR 0.54 (0.42-0.70)	1. Selection bias (uncertain diagnostic accuracy of HF in physician service file; insulin users excluded)	Metformin therapy in combination with sulfonylurea therapy was associated with substantial reductions in all-cause mortality and a trend towards reduced risk of all-cause hospitalization. Metformin therapy was not associated with an increased risk of lactic acidosis.
			2. All-cause mortality at study end	0.36 (0.30-0.45)	HR 0.61 (0.52-0.72)	2. uncertain exposure (cohort created based on a single prescription for antidiabetic medications; exposure to drug throughout follow-up uncertain; combination therapy not necessarily concurrent therapy)	
			2. All-cause hospitalization at 1 year	0.94 (0.78-1.15)	HR 0.92 (0.80-1.06)		
			3.All-cause hospitalization at study end	1.26 (1.01-1.56)	HR 0.93 (0.83-1.05)	3. Confounding by severity of diabetes or heart failure (no clinical data or functional status)	
			3. Combined all-cause mortality or hospitalization at 1 year	0.79 (0.65-0.96)	HR 0.86 (0.75-0.98)		
			4. Combined all-cause mortality or hospitalization at study end	0.70 (0.54-0.90)	HR 0.86 (0.77-0.96)		

Table 3.2. Continued...

Study	Study Agent (n)	Comparator (n)	Outcome	Unadjusted Risk Estimate (95% CI)	Adjusted Risk Estimate (95% CI)	Potential limitations and threats to validity*	Key findings and conclusion
Inzucchi et al., 2005[26]	TZDs (n=255)	No-insulin sensitizer (SU, nonSU secreatogoues, alpha-glucosidase inhibitors, insulin) (n=2,184)	1. All-cause mortality at 1 year	No absolute values reported	HR 1.04 (0.83-1.31)	1. selection bias (>65 years post MI only) 2. small sample size (few subjects in LV dysfunction subgroup) 3. uncertain exposure (cohort created based on discharge medications; exposure to drug throughout follow-up uncertain) 4. short duration of follow-up (1 yr outcomes)	In the subgroup of patients with LV dysfunction, TZDs did not increase the risk of mortality. There was a trend towards increasing risk for HF related hospitalizations for TZD therapy.
Masoudi et al. 2005[18]	TZDs (n=2,226)	No-insulin sensitizer (SU, nonSU secreatogoues, alpha-glucosidase inhibitors, insulin) (n=12,069)	1. All-cause mortality at 1 year 2. All-cause hospitalization at 1 year 3. HF readmission at 1 year	0.77 (0.70-0.84) 0.88 (0.80-0.97) 0.88 (0.80-0.97)	HR 0.87 (0.80-0.94) HR 1.04 (0.99-1.10) HR 1.06 (1.00-1.12)	1. selection bias (>65 years only) 2. uncertain exposure (cohort created based on discharge medications; exposure to drug throughout follow-up uncertain) 3. short duration of follow-up (1 yr outcomes)	TZD therapy associated with substantial reduction in mortality. No effect on all-cause hospitalization and a trend towards increased risk for HF related hospitalizations.
Masoudi et al. 2005[18]	Sulfonylurea (n=8,145)	NonSU secreatogoues, alpha-glucosidase inhibitors, insulin (n=8,272)	1. All-cause mortality at 1 year	No absolute values reported	HR 0.99 (0.91-1.08)	1. selection bias (>65 years only) 2. uncertain exposure (cohort created based on discharge medications; exposure to drug throughout follow-up uncertain) 3. short duration of follow-up (1 yr outcomes)	Sulfonylurea therapy not associated with an increase risk of mortality.

* - No study randomized patients to antidiabetic medications. Therefore, all studies are susceptible to confounding.
- SU –Sulfonylurea; TZD – Thiazolidinedione; HR – Hazards Ratio; HF – Heart Failure; MI – Myocardial Infarction; LV – Left Ventricular

Table 3.3: Results of test for statistical heterogeneity

Antidiabetic agent	Number of studies	Outcome Assessed	P Value for Heterogeneity	I^2 Statistic
Insulin	4	All-Cause Mortality	0.03	67.2%
	0	All-Cause Hospitalization	ND	ND
Thiazolidinediones	2	All-Cause Mortality	0.04	77.2%
	1	All-cause Hospitalization	ND	ND
Metformin	3	All-Cause Mortality at 1 year	<0.001	83.5%
	2	All-Cause Hospitalization at 1 Year	0.26	20.9%
Sulfonylurea	2	All-Cause Mortality at 1 Year	<0.001	96.4%

3.6 Reference List

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Appendix A. Search Strategy for Antidiabetic agent use in patients with heart failure and diabetes

Database	#	Terms	# Hits
Ovid MEDLINE(R) <1966 to February Week 2 2007>	1	exp Ventricular Dysfunction, Left/ or exp Cardiomyopathy, Dilated/ or exp Heart Failure, Congestive	69256
	2	exp Cardiomyopathies	50728
	3	exp Dyspnea	9701
	4	exp Edema, Cardiac/ or exp Edema	26547
	5	chronic heart failure.mp.	5737
	6	fluid retention.mp.	1441
	7	exp Diabetes Mellitus, Type 1/ or exp Diabetes Mellitus, Type 2/ or exp Diabetes Insipidus/ or exp Diabetes Mellitus	209879
	8	exp Metformin	2852
	9	exp Sulfonylurea Compounds	13053
	10	glyburide.mp. or exp Glyburide	4744
	11	gliclazide.mp. or exp Gliclazide	669
	12	glimepiride.mp.	361
	13	exp Tolbutamide	4472
	14	chlorpropamide.mp. or exp Chlorpropamide	1824
	15	exp Insulin/ or exp Insulin, Long-Acting/ or exp Insulin, Isophane	120896
	16	exp Thiazolidinediones	4013
	17	pioglitazone.mp.	1260
	18	rosiglitazone.mp.	1663
	19	troglitazone.mp.	1674
	20	exp Peroxisome Proliferator-Activated Receptors	2436
	21	exp Hypoglycemic Agents	139852
	22	Meglitinides.mp.	29
	23	repaglinide.mp.	330
	24	nateglinide.mp.	283
	25	meglitol.mp.	1
	26	acarbose.mp. or exp alpha-Glucosidases/ or exp Acarbose	3691
	27	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (309109)	309109
	28	1 or 2 or 3 or 4 or 5 or 6	143411
	29	27 and 28 (3501)	3501
	30	limit 29 to (addresses or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or "corrected and republished article" or dictionary or directory or duplicate publication or editorial or festschrift or government publications or guideline or historical article or in vitro or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or practice guideline or "retraction of publication" or retracted publication or "review" or "scientific integrity review" or technical report)	1299
	31	29 not 30	2202
	32	limit 31 to humans	1632

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Appendix A...continued

Database	#	Terms	# Hits
Ovid Healthstar <1966 to January 2007>	1	exp Ventricular Dysfunction, Left/ or exp Cardiomyopathy, Dilated/ or exp Heart Failure, Congestive	50924
	2	exp Cardiomyopathies	25732
	3	exp Dyspnea	5171
	4	exp Edema, Cardiac/ or exp Edema	7756
	5	chronic heart failure.mp.	4472
	6	fluid retention.mp.	817
	7	exp Diabetes Mellitus, Type 1/ or exp Diabetes Mellitus, Type 2/ or exp Diabetes Insipidus/ or exp Diabetes Mellitus	86046
	8	exp Metformin	1349
	9	exp Sulfonylurea Compounds	2592
	10	glyburide.mp. or exp Glyburide	821
	11	gliclazide.mp. or exp Gliclazide	221
	12	glimepiride.mp.	151
	13	exp Tolbutamide	617
	14	chlorpropamide.mp. or exp Chlorpropamide	309
	15	exp Insulin/ or exp Insulin, Long-Acting/ or exp Insulin, Isophane	25480
	16	exp Thiazolidinediones	1139
	17	pioglitazone.mp.	393
	18	rosiglitazone.mp.	494
	19	troglitazone.mp.	387
	20	exp Peroxisome Proliferator-Activated Receptors	435
	21	21 exp Hypoglycemic Agents	30126
	22	Meglitinides.mp.	10
	23	repaglinide.mp.	131
	24	nateglinide.mp.	114
	25	meglitol.mp.	0
	26	alpha glucosidase.mp. or exp alpha-Glucosidases	802
	27	1 or 2 or 3 or 4 or 5 or 6	81463
	28	exp Acarbose	314
	29	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 26 or 28 (102328)	102328
	30	27 and 29 (2025)	2025
	31	(addresses or bibliography or biography or comment or congresses or consensus development conference or consensus development conference, nih or "corrected and republished article" or dictionary or directory or duplicate publication or editorial or festschrift or guideline or historical article or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or practice guideline or published erratum or "retraction of publication" or retracted publication or "review" or "scientific integrity review").mp. [mp=title, original title, abstract, name of substance word, subject heading word]	174192 1
	32	30 not 31	1317
	33	limit 32 to humans	1312

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Appendix A...continued

Database	#	Terms	# Hits
EMBASE <1988 to 2007 Week 08>	1	exp Ventricular Dysfunction, Left/ or exp Cardiomyopathy, Dilated/ or exp Heart Failure, Congestive	36552
	2	exp Cardiomyopathies	25715
	3	exp Dyspnea	24876
	4	exp Edema, Cardiac/ or exp Edema	66998
	5	chronic heart failure.mp.	5418
	6	fluid retention.mp.	2826
	7	exp Diabetes Mellitus, Type 1/ or exp Diabetes Mellitus, Type 2/ or exp Diabetes Insipidus/ or exp Diabetes Mellitus	174728
	8	exp Metformin	8976
	9	exp Sulfonylurea Compounds	18539
	10	glyburide.mp. or exp Glyburide	9728
	11	gliclazide.mp. or exp Gliclazide	1619
	12	glimepiride.mp.	1349
	13	exp Tolbutamide	3598
	14	chlorpropamide.mp. or exp Chlorpropamide	1615
	15	exp Insulin/ or exp Insulin, Long-Acting/ or exp Insulin, Isophane	80949
	16	exp Thiazolidinediones/ (3176)	3176
	17	pioglitazone.mp.	3468
	18	rosiglitazone.mp.	4319
	19	troglitazone.mp.	3760
	20	exp Peroxisome Proliferator-Activated Receptors	2340
	21	exp Hypoglycemic Agents	108077
	22	Meglitinides.mp.	34
	23	repaglinide.mp.	1178
	24	nateglinide.mp.	889
	25	meglitol.mp.	1
	26	alpha glucosidase.mp. or exp alpha-Glucosidases	4420
	27	1 or 2 or 3 or 4 or 5 or 6	146712
	28	exp ACARBOSE	2593
	29	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 28	240432
	30	27 and 29	9877
	31	(book or conference paper or editorial or erratum or letter or note or proceeding or "review" or short survey).pt.	225831 2
	32	30 not 31	5154
	33	limit 32 to (amphibia or ape or bird or cat or cattle or chicken or dog or "ducks and geese" or fish or "frogs and toads" or goat or guinea pig or "hamsters and gerbils" or horse or monkey or mouse or "pigeons and doves" or "rabbits and hares" or rat or reptile or sheep or swine) (547)	547
	34	32 not 33	4607

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Appendix A...continued

Database	#	Terms	# Hits
CINAHL - Cumulative Index to Nursing, Allied Health Literature <1982 to February Week 4 2007>	1	chronic heart failure.mp.	959
	2	fluid retention.mp.	91
	3	chlorpropamide.mp. or exp Chlorpropamide	7
	4	pioglitazone.mp.	148
	5	rosiglitazone.mp.	185
	6	troglitazone.mp.	95
	7	Meglitinides.mp.	10
	8	repaglinide.mp.	31
	9	nateglinide.mp.	29
	10	congestive heart failure.mp. [mp=title, subject heading word, abstract, instrumentation]	6775
	11	left ventricular dysfunction.mp. [mp=title, subject heading word, abstract, instrumentation]	1026
	12	cardiomyopathy.mp. [mp=title, subject heading word, abstract, instrumentation]	1096
	13	dyspnea.mp. [mp=title, subject heading word, abstract, instrumentation] (2372)	2372
	14	fluid retention.mp. [mp=title, subject heading word, abstract, instrumentation]	91
	15	cardiomyopathies.mp. [mp=title, subject heading word, abstract, instrumentation]	45
	16	heart failure.mp. [mp=title, subject heading word, abstract, instrumentation]	7820
	17	cardiac failure.mp. [mp=title, subject heading word, abstract, instrumentation]	1012
	18	edema.mp. [mp=title, subject heading word, abstract, instrumentation]	3047
	19	1 or 2 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (14219)	14219
	20	metformin.mp. [mp=title, subject heading word, abstract, instrumentation]	604
	21	glyburide.mp. [mp=title, subject heading word, abstract, instrumentation]	120
	22	gliclazide.mp. [mp=title, subject heading word, abstract, instrumentation]	23
	23	glimepiride.mp. [mp=title, subject heading word, abstract, instrumentation]	41
	24	sulfonylurea.mp. [mp=title, subject heading word, abstract, instrumentation]	317
	25	insulin.mp. [mp=title, subject heading word, abstract, instrumentation]	15725
	26	hypoglycemic agents.mp. [mp=title, subject heading word, abstract, instrumentation]	1391
	27	thiazolidinediones.mp. [mp=title, subject heading word, abstract, instrumentation]	177
	28	peroxisome proliferator activated receptors.mp. [mp=title, subject heading word, abstract, instrumentation]	12

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29	tolbutamide.mp. [mp=title, subject heading word, abstract, instrumentation]	28
30	alpha glucosidase.mp. [mp=title, subject heading word, abstract, instrumentation]	52
31	acarbose.mp. [mp=title, subject heading word, abstract, instrumentation]	119
32	meglitol.mp. [mp=title, subject heading word, abstract, instrumentation]	0
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34	thiazolidinedione$.mp. [mp=title, subject heading word, abstract, instrumentation]	211
35	diabetes.mp. [mp=title, subject heading word, abstract, instrumentation]	28230
36	3 or 4 or 5 or 6 or 7 or 8 or 9 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 33 or 34 or 35	31795
37	19 and 36	886
38	(abstract or accreditation or "advice and referral website" or algorithm or anecdote or audiovisual or bibliography or biography or book or brief item or care plan or cartoon or ceu or chat groups or classification term or "cod of ethics" or commentary or commercial website or computer program or consumer patient teaching materials or corrected article or critical path or diagnostic images or directories or editorial or equations & formulas or exam questions or forms or games or glossary).pt.	427420
39	(historical material or interview or individual testimonial website or information website or journal description or legal cases or letter or listservs or nurse practice acts or obituary or overall or pamphlet or pamphlet chapter or pictorial or poetry or practice acts or practice guidelines or proceedings or protocol or "questionnaire/scale" or questions & answers or research instrument or research term definition or response or "review" or search strategy or software or standards or "systematic review" or teaching materials or tracings or website).pt.	350221
40	38 or 39	670671
41	37 not 40	508

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Appendix A...continued

Database	#	Terms	# Hits
International	1	chronic heart failure.mp.	324
Pharmaceutical	2	fluid retention.mp.	119
Abstracts	3	chlorpropamide.mp. or exp Chlorpropamide	294
<1970 to Februrary	4	pioglitazone.mp.	252
2007>	5	rosiglitazone.mp.	292
	6	troglitazone.mp.	201
	7	repaglinide.mp.	108
	8	nateglinide.mp.	88
	9	congestive heart failure.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	1608
	10	left ventricular dysfunction.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	179
	11	cardiomyopathy.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	369
	12	dyspnea.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	538
	13	fluid retention.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	119
	14	cardiomyopathies.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	12
	15	heart failure.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	3470
	16	cardiac failure.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	250
	17	edema.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	2158
	18	1 or 2 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	6447
	19	metformin.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	782
	20	glyburide.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	562
	21	gliclazide.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	99
	22	glimepiride.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	101
	23	sulfonylurea.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	339
	24	insulin.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	5805
	25	tolbutamide.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	393
	26	alpha glucosidase.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	100
	27	acarbose.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	189

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28	meglitol.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	0
29	meglitinide$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	30
30	thiazolidinedione$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	320
31	diabetes.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	7908
32	hypoglycemic agent$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	365
33	hypoglycaemic agent$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	18
34	peroxisome proliferator activated receptor$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	104
35	alpha glucosidase inhibitor$.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]	86
36	3 or 4 or 5 or 6 or 7 or 8 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 29 or 30 or 31 or 32 or 33 or 34 or 35	12000
37	36 and 18	420
38	limit 37 to human	352

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Appendix A...continued

Database	#	Terms	# Hits
AMED (Allied and Complementary Medicine) <1985 to March 2007>	1	exp Edema, Cardiac/ or exp Edema	150
	2	chronic heart failure.mp.	103
	3	fluid retention.mp.	9
	4	exp Diabetes Mellitus, Type 1/ or exp Diabetes Mellitus, Type 2/ or exp Diabetes Insipidus/ or exp Diabetes Mellitus	1444
	5	glyburide.mp. or exp Glyburide	0
	6	gliclazide.mp. or exp Gliclazide	2
	7	glimepiride.mp.	0
	8	chlorpropamide.mp. or exp Chlorpropamide	8
	9	exp Insulin/ or exp Insulin, Long-Acting/ or exp Insulin, Isophane	152
	10	pioglitazone.mp.	2
	11	rosiglitazone.mp.	5
	12	troglitazone.mp.	6
	13	exp Hypoglycemic Agents	313
	14	Meglitinides.mp.	0
	15	repaglinide.mp.	1
	16	nateglinide.mp.	0
	17	meglitol.mp.	0
	18	alpha glucosidase.mp. or exp alpha-Glucosidases	17
	19	ventricular dysfunction.mp. or exp Heart ventricle	63
	20	exp Heart failure congestive/ or heart failure.mp.	432
	21	cardiomyopathy.mp. or exp cardiomyopathies	52
	22	chronic heart failure.mp.	103
	23	cardiac failure.mp.	17
	24	metformin.mp.	12
	25	Peroxisome Proliferator-Activated Receptors.mp.	2
	26	26 thiazolidinedione$.mp.	1
	27	tolbutamide.mp.	19
	28	sulfonylurea.mp.	5
	29	acarbose.mp.	6
	30	4 or 6 or 8 or 9 or 10 or 11 or 12 or 13 or 15 or 18 or 24 or 25 or 26 or 27 or 28 or 29	1695
	31	1 or 2 or 3 or 19 or 20 or 21 or 22 or 23	693
	32	30 and 31	5

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Appendix A...continued

Database	#	Terms	# Hits
EBM Reviews -	1	chronic heart failure.mp.	1050
Cochrane Central	2	fluid retention.mp.	204
Register of	3	chlorpropamide.mp. or exp Chlorpropamide	105
Controlled Trials	4	pioglitazone.mp.	156
<1st Quarter 2007>	5	rosiglitazone.mp.	196
	6	troglitazone.mp.	138
	7	Meglitinides.mp.	1
	8	repaglinide.mp.	80
	9	nateglinide.mp.	59
	10	congestive heart failure.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	2184
	11	left ventricular dysfunction.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	571
	12	cardiomyopathy.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	916
	13	dyspnea.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1381
	14	fluid retention.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	204
	15	cardiomyopathies.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	152
	16	heart failure.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	5757
	17	cardiac failure.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	372
	18	edema.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	3227
	19	1 or 2 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	11152
	20	metformin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	775
	21	glyburide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	424
	22	gliclazide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	138
	23	glimepiride.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword])	105
	24	sulfonylurea.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	576
	25	insulin.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	11766
	26	hypoglycemic agents.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	1972
	27	thiazolidinediones.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	414
	28	peroxisome proliferator activated receptors.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	12

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29	tolbutamide.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	194
30	alpha glucosidase.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	162
31	acarbose.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	243
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34	thiazolidinedione$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	419
35	diabetes.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	10880
36	3 or 4 or 5 or 6 or 7 or 8 or 9 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 33 or 34 or 35	17488
37	19 and 36	528
38	acarbose.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	243
39	38 and 19	3
40	39 or 37	528
41	limit 40 to (abstract or addresses or bibliography or biography or comment or conference or congresses or consensus development conference or "corrected and republished article" or duplicate publication or editorial or guideline or historical article or interview or lectures or letter or monograph or news or practice guideline or published erratum or retracted publication or "review" or "review literature" or "review of reported cases" or review, academic or review, multicase or review, tutorial)	8
42	40 not 41	520

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Appendix A...continued

Database	#	Terms	# Hits
Web of Science; DocType=Article; Language=All	1	TS=(congestive heart failure OR left ventricular dysfunction OR cardiomyopath* OR heart failure OR cardiac failure OR chronic heart failure OR dyspnea OR edema OR fluid retention)	>10000 0
languages;Databases= SCI- EXPANDED, SSCI,; Time span=1900-2006	2	TS=(diabetes OR diabetes Mellitus OR type 1 diabetes OR type 1 diabetes OR type I diabetes OR Insulin dependent diabetes OR type 2 diabetes OR type II diabetes OR non-insulin dependent diabetes OR noninsulin dependent diabetes OR Metformin OR Sulfonylurea Compounds OR Glyburide OR gliclazide OR Gliclazide OR glimepiride OR Tolbutamide OR Chlorpropamide OR Insulin OR Thiazolidinedione* OR pioglitazone OR rosiglitazone OR troglitazone OR Peroxisome Proliferator-Activated Receptor* OR Hypoglycemic Agent* OR hypoglycaemic agent* OR Meglitinide* OR Repaglinide OR nateglinide OR meglitol OR acarbose OR alpha-Glucosidase* OR Alpha glucosidase inhibitor*)	>10000 0
	3	#2 AND #1	7453
	4	TS=(MICE OR CAT* OR RAT* OR DOG* OR PORCINE OR PIG* OR CAT* OR RABBIT* OR MOUSE OR ZUCKER OR ANIMAL)	>10000 0
	5	#3 NOT #4	2825
	6	TS=REVIEW	>10000 0
	7	TS=(RENAL OR NEPHROPATHY OR UROLOGY OR SEXUAL OR OCULAR OR EYE OR RETINAL OR OPTHALMIC OR FOOT OR FEET OR NEUROPATHY OR NERVE OR NERVOUS OR DEPRESSION OR MENTAL OR ONCOLOGY OR CANCER OR HEMATOLOGY OR BIOLOGY OR CELL BIOLOGY OR CHEMISTRY OR MEDICINAL CHEMISTRY OR REHABILITATION OR ORTHOPEDICS OR BONE OR BIOPHYSICS OR GENE* OR GENETIC* OR HEREDITARY OR CHROMOSOME OR PROTEIN OR INFANT* OR CHILD* OR PEDIATRIC* OR BABY OR ECONOMIC OR RESOURCE UTILIZATION OR HEALTH CARE UTILIZATION OR ENGINEERING OR ELECTRICAL OR TRANSDUCTION)	>10000 0
	8	#5 NOT #6	2647
	9	#8 NOT #7	1017

CHAPTER 4: WHEN SCIENTIFIC EQUIPOSE MEETS CLINICAL REALITY: THE CASE OF METFORMIN FOR PATIENTS WITH DIABETES AND HEART FAILURE

4.1 Abstract

Objective: As there is controversy as to the benefits of metformin in patients with heart failure (HF), we designed and implemented a pilot study to evaluate the feasibility of conducting a large randomized controlled trial of metformin in patients with HF and type 2 diabetes.

Study Design: The pilot study was a prospective, randomized double blinded placebo controlled trial. Patients with HF diagnosed by a physician and type 2 diabetes were screened in a tertiary care hospital, a community care hospital, and a specialized heart failure clinic in Edmonton, Alberta, Canada. Exclusion criteria included the current use of insulin or high dose metformin, decreased renal function, or a glycosylated hemoglobin <7%. Patients were to be randomized to 1500mg of metformin daily or matching placebo and followed for 6 months for a variety of functional outcomes, as well as clinical events.

Results: Fifty-eight patients were screened over a six month period with no patients being enrolled in the trial. Due to the high exclusion rates, the pilot study was abandoned. The mean age of screened patients was 77 (SD 9) years and 57% were male. The main reasons for exclusion were: use of insulin therapy (n=23; 40%), glycosylated hemoglobin <7% (n=17; 29%) and current use of high dose metformin (n=12; 21%). Overall, metformin therapy was the most commonly prescribed oral antihyperglycemic agent (n=27; 51%). On average, patients were receiving 1,706mg (SD 488mg) of metformin daily with the majority using metformin as monotherapy.

Conclusion: Despite the appearance of uncertainty in the literature, there does not appear to be clinical uncertainty with regards to the use of metformin, thus making a definitive randomized trial virtually impossible. *ClinicalTrials.gov Identifier: NCT00325910*

4.2 Introduction

Metformin has been approved for use in the treatment of type 2 diabetes mellitus for nearly 3 decades in Europe and Canada and for a decade in the United States (US). Numerous studies have shown metformin to be highly effective and safe in the treatment of type 2 diabetes.[1-3] Metformin is the only antidiabetic agent that has been shown to reduce mortality in patients newly diagnosed with type 2 diabetes and the only antidiabetic agent not shown to be associated with increased morbidity and mortality in patients with cardiac disease, including heart failure.[2-5]

However, product labeling for metformin in Canada and the US indicates that it is contraindicated in most patients with heart failure.[6,7] Diabetes is a common comorbidity in patients with heart failure and portends a particularly poor prognosis.[8,9] As such, significant proportion of patients with diabetes may be potentially denied a beneficial treatment. It is thus not surprising that there is a vigorous debate in the literature about whether or not metformin should be used in patients with heart failure and type 2 diabetes.[4,7,10-23]

Although two recent population-based epidemiologic studies have suggested that, compared to other antidiabetic medications, metformin may be beneficial in patients with heart failure and diabetes, both studies recommended confirmation of their findings in randomized trials.[4,16] Given the robust debate in the literature about the role of metformin in heart failure, this appears to be a question that needs to be resolved in a randomized controlled trial.[24]

Thus, we designed and implemented a pilot study, PHANTOM (Patients with Heart Failure ANd Type 2 Diabetes Treated with Placebo Or Metformin), to evaluate the feasibility of a large randomized controlled trial of metformin in patients with heart failure and type 2 diabetes (*ClinicalTrials.gov Identifier: NCT00325910).*

4.3 Methods

Study Design. A description of the full study protocol is found in Appendix B. Briefly, the PHANTOM pilot study was a multi-centre, prospective randomized blinded placebo controlled trial designed to examine functionality, morbidity, and mortality outcomes in patients with heart failure and diabetes mellitus who are treated with metformin therapy

over a 6 month period. Two hospitals, the University of Alberta Hospital and the Misericordia Hospital, and one outpatient specialized heart failure clinic within the Capital Health Region (Edmonton, Alberta, Canada) participated in the study. The Capital Health Region is one of the largest integrated health delivery systems in Canada serving over 1 million people.[25] The University of Alberta Hospital is an 800-bed tertiary university-based teaching hospital and has been a recruitment site for many major cardiovascular trials including the Digitalis Investigation Group (DIG) Trial, the Heart Outcomes Prevention Evaluation (HOPE) Study, the Studies of Left Ventricular Dysfunction (SOLVD), and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trials. The Misericordia Hospital is a 500-bed community hospital also involved in several large randomized trials in acute coronary syndromes and heart failure. The study protocol was reviewed and approved by the Research Ethics Board of all participating sites.

Eligibility. We screened consecutive patients older than 18 years, admitted to the hospital or emergency room or registered patients of the heart failure clinic. Inclusion criteria were: physician diagnoses of symptomatic heart failure (NYHA class II, III, IV) and type 2 diabetes (i.e., a previous physician diagnosis or actively receiving oral antidiabetic agents or a new diagnosis of type 2 diabetes, defined as a fasting blood glucose $\geq$7.0 mmol/L or random blood glucose $\geq$11.1 mmol/L, and accompanied by acute metabolic decompensation or 2 hour plasma glucose in a 75 gram oral glucose tolerance test $\geq$11.1 mmol/L).[26] We excluded patients if they were receiving greater than 1500 mg of metformin daily, were unwilling to change their antidiabetic regimens, were receiving insulin therapy, had a serum creatinine $\geq$ 180 μmol/L, had an A1c < 7.0%, were unable to communicate because of language barriers, had dementia or mental illness, were unwilling to complete self-monitoring of serum blood sugars during the trial period, were participating in another heart failure or diabetes clinical trial involving medications, or had significant comorbidities or a terminal illness precluding them from following the trial protocol over the 6 month follow-up period.

Screening. Potential patients were identified through referrals of hospitalized or heart failure clinic patients. After identification, a two-stage screening process began. In stage 1, potentially eligible individuals were screened for non-invasive inclusion/exclusion criteria (i.e., all exclusion criteria except A1c and serum creatinine). In stage 2, patients who were not excluded after stage 1 were approached for consent to a blood sample to determine A1c and serum creatinine eligibility (if not previously completed as part of their clinic or hospital medical care). Eligible patients meeting all inclusion and exclusion criteria and consenting to the trial continued with the study protocol (Appendix C).

Randomization and study procedures. Consenting patients were to be randomized to either metformin or matching placebo tablets in a 1:1 ratio. Randomization was planned through a secure website provided by the project office (Epidemiology Coordinating and Research (EPICORE) Centre, University of Alberta)

Patients were to be assessed at baseline and six months later, with monthly telephone contact to assess response to the study medication and ascertain clinical outcomes. Follow-up visits and blood testing (i.e., A1c and serum creatinine) were planned for 3 and 6 month visits (Appendix C). We planned a dosage titration protocol (Appendix D) where patients would be instructed to slowly titrate their study medication to a maximum dose of 1500mg per day over a 3 week period based on a published titration protocol.[1]

Study Endpoints and Statistical Analysis. The primary outcome was a combined endpoint of all-cause mortality or all-cause hospitalization. As secondary endpoints, comparisons of mean change in A1c, six minute walk distance, and mean change in health-related quality of life (i.e., RAND-12, EQ-5D, and Kansas City Cardiomyopathy Questionnaire) scores from baseline to the 6 month follow-up visit were also planned.

We established criteria for monitoring safety of metformin, to identify patients developing lactic acidosis requiring urgent medical attention, as defined as an emergency room visit or hospitalization.

We anticipated the full study would require a sample size of 1000 patients with heart failure and diabetes to detect an absolute difference in event rates of at least 10% based on an incidence rate of 50%[27] in our primary outcome per year with a two-tailed alpha = 0.05 and beta = 0.10. The goal of the pilot study was to enroll 100 patients.

4.4 Results

Recruitment for the study began May 1, 2006. As of October 15th, 2006, fifty-eight consecutive patients with diabetes and heart failure were screened through the outpatient ambulatory heart failure clinic (n=8, 14%) and in-patient cardiology and general medical wards (n=50, 86%) with no patients meeting eligibility criteria. Using a conservative estimate of 1 patient enrolled for every 10 patients screened, our data suggests that the likelihood that a significant number of potentially eligible patients were missed during screening would be less than 5%. This poor availability of suitable patients led the Steering Committee to recommend that the study be abandoned on October 17, 2006.

The characteristics of the individuals screened for the pilot study are shown in Table 4.1. Of note, 5 patients refused to have their screening data collected and are therefore not included in our results. Of the patients admitted to hospital (n=45, 85%), heart failure (n=22, 49%) was the most common admitting diagnosis. Acute coronary syndromes (n=7, 16%) and diabetes (n=4 (9%) were the next most common reasons for admission. The median length of stay in hospital was 12 days (interquatrile range 9 to 36).

Overall, the patients screened represented a typical population of patients with heart failure with 57% males and an average age of 77 (SD 9) years. At the time of screening, 51 (96%) patients were receiving an angiotensin converting enzyme (ACE) inhibitor or angiotension receptor blockers (ARB) (Table 4.1). Approximately two-thirds of patients were also receiving beta-blockers, antiplatelet and lipid-lowering therapies with 27 (51%) patients receiving all three therapies.

The use of insulin (n=23, 43%) was the most common reason for trial exclusion (Figure 4.1). Of the patients receiving insulin therapy, 9 (39%) had additional exclusion criteria. Overall, 11 (48%) patients received insulin in combination with oral antidiabetic agents. The second most common reason for exclusion from the trial was an A1c value

less than 7%. Of the patients who had an A1c available (n=34, 64%), 17 (50%) patients were excluded with an A1c less than 7% reported in their medical records (Figure 4.1). The mean A1c was 7.3% (SD 2) (Table 4.1). This may misrepresent the true A1c values, however, as not all patients had an A1c measured due to the two stage screening protocol.

Despite being 'absolutely' contraindicated in this population, metformin was the most commonly prescribed oral antidiabetic agent with 27 (51%) patients receiving it at the time of screening (Table 4.2). In comparison, few patients were receiving therapy with sulfonylureas, thiazolidinediones, meglitinides, or alpha glucosidase inhibitors (Table 4.1). Of the patients receiving metformin, 12 (44%) were receiving greater than 1500mg per day and were therefore excluded from our study (Figure 4.1). On average, patients were receiving 1,706mg per day (SD 488) with 2000mg per day as the most common daily dose. Twelve (44%) patients used metformin as monotherapy, 9 (33%) in combination with other oral agents and 6 (22%) in combination with insulin alone (Table 4.1). Metformin was also more commonly prescribed in combination with insulin than other oral agents. Of the 23 patients receiving insulin therapy, 8 (35%) were also prescribed metformin. We saw no significant differences between patients receiving metformin and non-metformin regimens in terms of clinical or demographic characteristics (Table 4.2).

4.5 Discussion

A guiding principle for the conduct of a randomized controlled trial is that of equipoise, or perhaps more appropriately 'uncertainty' as to whether the therapy under study works.[24] Although metformin has been demonstrated to improve outcomes, its use in people with heart failure and type 2 diabetes is a contentious issue. Editorialists have argued both sides of the patient safety coin for use of metformin in high risk patients, providing strong evidence for the criterion of uncertainty[4,7,10-23] Results of our pilot study would suggest, however, that there may be discordance between the scientific community and clinicians.

Although it is clear from the scientific literature that there is uncertainty with respect to the efficacy of metformin in patients with heart failure, over 50% of patients with diabetes and heart failure in our pilot study were receiving metformin, either alone or in combination with other antidiabetic agents, suggesting there is no uncertainty in the eyes of clinicians. Although this may be surprising, one must consider that metformin therapy is one of the most commonly prescribed antidiabetic agents and has a long history of use in Canada. Indeed, a recent population based study using Canadian data suggested that two-thirds of all patients with type 2 diabetes treated with antidiabetic medications receive metformin therapy, either alone or in combination with other agents.[28] Furthermore, observational data in Canada, Europe, and the US have shown that 20 to 25% of patients receiving metformin therapy also have comorbid heart failure[4,10,16,19,22,29,30] It is also known that the proportion of patients receiving metformin therapy has increased over time and with it the proportion of people with heart failure and type 2 diabetes who use metformin. A large observational study using US Medicaid Beneficiary data indicated that the use of metformin increased by 56% in patients with heart failure between 1998-99 and 2000-01.[11] In our pilot study, half of all subjects were actively receiving metformin therapy. Furthermore, the majority of people were receiving relatively high doses of metformin therapy (i.e., >1500mg/day). Given the accumulated research, including our pilot data, it would seem there is little uncertainty to the use of metformin in patients with heart failure at the individual clinician level.

Should there be uncertainty with regards to the use of metformin in patients with heart failure? Perhaps not, considering the evidence base for the efficacy of metformin in type 2 diabetes. Indeed, numerous observational and randomized controlled studies have clearly shown metformin to be highly efficacious for patients with type 2 diabetes.[1-4,16] The potential scientific uncertainty with using metformin in patients with heart failure seems to be focused on the risks rather than the benefits. Although metformin associated lactic acidosis is a rare event, uncertainty around its safety would suggest that a randomized controlled trial is warranted. It is well known, however, that randomized controlled trials are, by design, ill suited to address the issue of safety, especially when rare events are concerned.[31,32] If safety is the main concern, a large, well designed, phase 4, prospective evaluation of metformin use in patients with heart failure may provide the best evidence.[31,32]

The inability to enroll patients into the pilot study may have been influenced by numerous factors including the patient-clinician relationship and the perceived importance of the trial.[33] It is possible, for example, that admitting the potential uncertainty of using metformin in heart failure by the clinician may be perceived as damaging to the patient-clinician relationship; thereby becoming a barrier to patient enrollment.[34,35] Although all clinicians directly involved in our study were supportive, clinicians outside of the study may have been less receptive, which may have affected patient referral to the study. It is also possible clinicians outside of the study did not feel the research question was of interest or importance.[36] Although metformin is "absolutely contraindicated" in this population, individual clinicians prescribing for these patients presumably felt that the potential benefits outweighed any potential risks, and may have felt uneasy with the potential withdrawal of metformin therapy. If this is indeed the case, even if a successful randomized control trial is conducted, will it substantially alter prescribing patterns of the front line clinician? Numerous examples exist in the literature where randomized controlled trials have changed the collective thinking of the scientific community but have failed to make significant impacts on the prescribing patterns of individual clinicians.[37]

Our experience should be viewed in light of several other considerations. It is possible that the patients who were actively screened were atypical heart failure and type

2 diabetes patients. For example, healthier subjects who may not have required metformin therapy or only required low dose metformin may not have been referred to the outpatient specialized heart failure clinic. Although the possibility exists, we feel the population screened was very similar to the those studied in both recent population-based observational studies, suggesting that selection bias was not a factor.[4,16]

In addition, as with any clinical trial, the inclusion and exclusion criteria clearly affected potential enrollment. We feel, however, few modifications could be made to our liberal inclusion criteria, requiring only a physician diagnosis of heart failure and type 2 diabetes. Previous metformin use was not an exclusion criteria but patients receiving high dose metformin therapy (>1500mg/day) were excluded as it was considered unethical to potentially randomize patients to placebo for a medication previously deemed necessary by a physician. Similarly, patients with adequate control of their diabetes (i.e., A1c <7%) were also excluded as it was deemed unethical and potentially unsafe to initiate another antidiabetic therapy. With respect to renal function, the current product monograph recommends that metformin be avoided in patients with a creatinine clearance <60mL/min.[6] In our study, the criteria was considerably more liberal, allowing patients with renal function as low as 20-30mL/min.

Lastly, patients using insulin therapy were excluded. Previous research has suggested that insulin therapy may be associated with an increased risk of heart failure[9,38] and also an increased risk of mortality in people with diabetes and heart failure.[5,39,40] We therefore felt it was important to exclude this treatment, to focus on the effects of metformin. Even if we had not excluded insulin users, 39% of these patients would not have been eligible due to other exclusions. As a result, changes in the inclusion and exclusion criteria would likely have not significantly altered our study outcome.

In summary, our pilot data suggest that many physicians are using metformin as a key component of the glucose lowering regimen in patients with heart failure and type 2 diabetes and thus, a large randomized trial will be an extremely difficult undertaking. Given the already frequent and increasing clinical experience of using metformin in patients with heart failure, a trial design which limits the use of metformin therapy may have difficulties in gaining clinician commitment as clinical uncertainty does not appear to exist.[24] To ensure optimal prescribing, it is essential that revisions to indications and

contraindications of drug therapies are made on a continual basis as new evidence becomes available. In our current system, although precautions and contraindications are often easily added to drug monographs, the removal of these same concerns rarely occurs. Currently available data suggests that metformin may be appropriate in patients with treated, compensated ventricular dysfunction and adequate renal function.[7] Failure to re-evaluate the current prescribing guidelines for metformin therapy may result in suboptimal prescribing practices in people with heart failure. Like others [7,12,18], we believe that the current contraindications of metformin therapy in people with heart failure need to be re-evaluated and concur that metformin should be considered 'innocent until proven guilty'.[7]

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Table 4.1: Clinical Characteristics of Screened Patients

Characteristic (n=53)*	No. (%) or Mean ± SD
Age – yrs	76.5 ± 8.6
Sex – male	30 (57)
Serum Creatinine (μmol/L)	135 ± 64
A1c (%)†	7.3 ± 0.02
Heart Failure Medications	
Beta-Blockers	38 (72)
ACE Inhibitors or ARBs	51 (96)
Calcium Channel Blockers	18 (34)
Antiplatelet Agents	44 (83)
Digoxin	9 (17)
Spironolactone	12 (23)
Lipid Therapy	41 (77)
Nitrates	10 (19)
Diabetes Medications	
Insulin	23 (43)
Metformin	27 (51)
Monotherapy	12
Combination with other oral agents	9
Insulin alone	6
Sulfonylureas	8 (15)
Thiazolidinediones	4 (8)
Meglitinides	2 (4)
Acarabose	0 (0)

* - five patients refused to have data included
† - 34 people had A1c assessed in previous 3 months

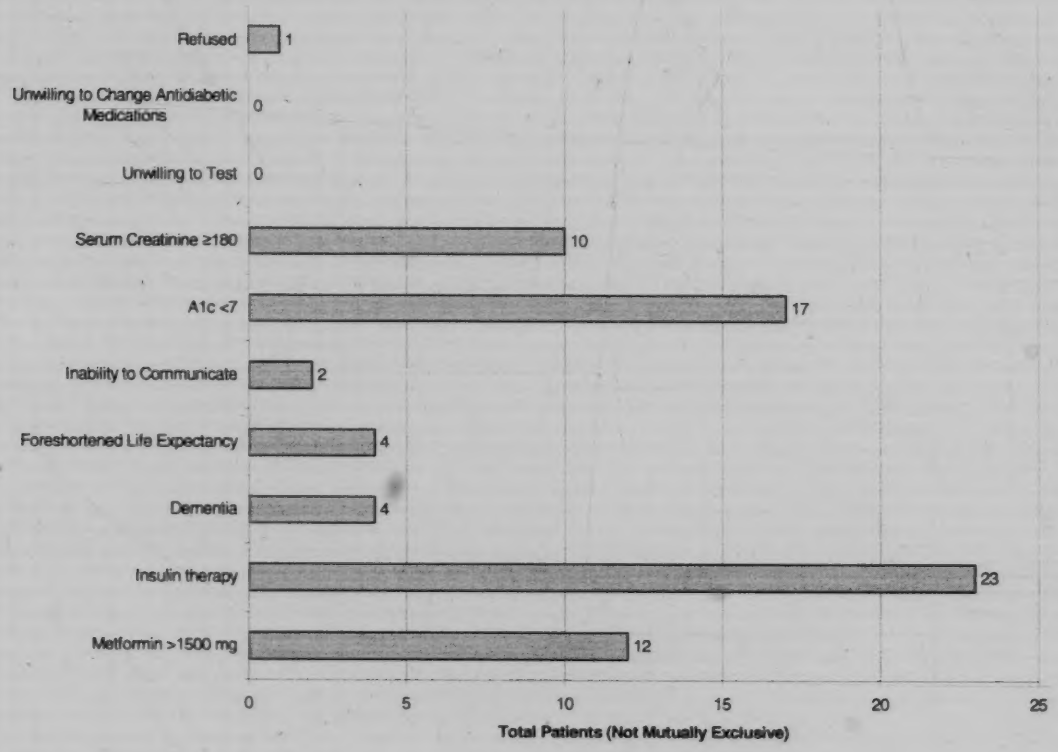
Table 4.2: Comparison of Metformin and Non-Metformin Users

Characteristic*	Non-Metformin User (n=26)	Metformin User (n=27)	P-value
	No. (%) or Mean ± SD		
Age – yrs	78.2 ± 8.5	74.9 ± 8.7	0.17
Sex – male	16 (62)	14 (52)	0.48
Serum Creatinine (μmol/L)	147 ± 75	123 ± 49	0.17
A1c (%)†	6.8 ± 1.2	7.7 ± 2.6	0.22
Heart Failure Medications			
Beta-Blockers	18 (69)	20 (74)	0.70
ACE Inhibitors or ARBs	26 (100)	25 (93)	0.49
Calcium Channel Blockers	8 (31)	10 (37)	0.63
Antiplatelet Agents	21 (81)	23 (85)	0.73
Digoxin	4 (15)	5 (19)	1.0
Spironolactone	5 (19)	7 (26)	0.56
Lipid Therapy	19 (73)	22 (82)	0.47
Nitrates	4 (15)	6 (22)	0.73
Diabetes Medications			
Insulin	15 (58)	8 (30)	0.039
Sulfonylureas	3 (12)	5 (19)	0.70
Thiazolidinediones	1 (4)	3 (11)	0.61
Meglitinides	1 (4)	1 (4)	1.00
Acarabose	0 (0)	0 (0)	0 (0)

* - five patients refused to have data included

† - 15 people in non-metformin user and 19 people in metformin user groups

Figure 4.1. Reason for Study Exclusion



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outcomes from the Assessment of Treatment with Lisinopril and Survival (ATLAS) study. *Clin Ther.* 2004;26:694-703.

Appendix B: PHANTOM Study Protocol

Study Purpose and Hypotheses

Purpose

To conduct a pilot study to evaluate the feasibility of a large randomized controlled trial (RCT) of metformin in patients with heart failure and type 2 diabetes and to generate initial morbidity and mortality estimates in this patient population.

Hypotheses

The specific hypotheses to be tested are as follows:

Primary hypothesis

a) Subjects with heart failure and type 2 diabetes who receive metformin will have a significant reduction in the combined endpoint of all-cause mortality and all-cause hospitalization as compared to subjects who receive placebo therapy.

Secondary Hypotheses

a) Subjects with heart failure and type 2 diabetes who receive metformin will have a significant reduction in all-cause mortality compared to subjects who receive placebo.

b) Subjects with heart failure and type 2 diabetes who receive metformin will have a significant reduction in all-cause hospitalization as compared to subjects who receive placebo.

c) Subjects with heart failure and type 2 diabetes who receive metformin will have a significant improvement in the six minute walk test as compared to subjects who receive placebo.

d) Subjects with heart failure and type 2 diabetes who receive metformin will have a significant improvement in A1c as compared to subjects who receive placebo.

e) Subjects with type 2 diabetes and heart failure who receive metformin will be at similar risk for the development of lactic acidosis requiring urgent medical attention, as defined as an emergency room visit or hospitalization for lactic acidosis, as compared to subjects who receive placebo.

f) Subjects with heart failure and type 2 diabetes who receive metformin will have clinically important improvements in health related quality of life (HRQL) as measured by the EQ5D and the Kansas City Cardiomyopathy Questionnaire (KCCQ) as compared to subjects who receive placebo.

Methods

Study Design

A multi-centre prospective triple blinded randomized placebo controlled trial (RCT) design. Subjects will be recruited through heart function clinics or inpatient hospital admissions/emergency room visits in the Capital Health Region. Subjects will be randomly allocated to either metformin or placebo and will be prospectively followed for 6 months from the time of enrollment.

Subjects

Inclusion Criteria:

All subjects with physician-diagnosed symptomatic heart failure (NYHA class II, III, IV) and type 2 diabetes.

A diagnosis of type 2 diabetes defined as:

i) a previous physician diagnosis of type 2 diabetes as documented in the subject's clinical record or;
ii) receiving oral antihyperglycemic agents or;
iii) a new diagnosis of type 2 diabetes during the visit within the heart failure clinic or hospital based on a fasting blood glucose $\geq$7.0 mmol/L or random blood glucose $\geq$11.1 mmol/L accompanied by acute metabolic decompensation or 2 hour plasma glucose in a 75 gram oral glucose tolerance test $\geq$11.1 mmol/L.[26]

Exclusion Criteria:

All subjects with the following conditions will be excluded from the study:

i) subjects currently receiving greater than 1500 mg of metformin therapy per day
ii) subjects who are unwilling to change their antidiabetic regimens;
iii) subjects receiving insulin therapy;
iv) serum creatinine $\geq$ 180 µmol/L;
v) A1c < 7.0 percent;
vi) inability to communicate (language barrier);
vii) dementia/mental illness;
viii) age < 18 years;
ix) subjects unwilling to complete self-monitoring of serum blood sugars during the trial period.
x) those participating in another heart failure or diabetes clinical trial involving medication;
xi) severe comorbidities or foreshortened life expectancy;
xii) subjects who do not provide written informed consent to participate.

Procedures

Local research physicians and nurses will identify potential subjects for inclusion in our study through hospitals located in the Capital Health Region. Subjects will be identified by the local research coordinator through local medical clinics or inpatient admissions/emergency room visits. Potential subjects will be approached by the research coordinator for verbal consent to review their medical chart records for potential enrollment in our study. For potentially eligible individuals with a confirmed diagnosis of heart failure and type 2 diabetes recorded in the medical records, verbal and written information from the local research physician or the research coordinator regarding the study's purpose, procedures, risks/benefits, confidentiality, and contact information will be provided. Subjects willing to enroll in the study will subsequently be asked to provide written informed consent. In the event the subject is discharge from the hospital or emergency room department prior to receiving information regarding potential enrollment in the study, the research coordinator will contact subjects to determine if they are interested in the study. Subjects interested in the study will be asked to arrange an in-person follow-up visit at one of the two heart function clinics to discuss the study further, as mentioned above, and to provided written informed consent.

Once consent has been received, the subjects' baseline laboratory blood work will be reviewed and collected to determine study eligibility from the medical records. Specifically, an A1c and a chemistry profile will be collected (Appendix B). The cost of these additional laboratory blood tests will be covered through the study budget. In subjects with elevated laboratory values (e.g., potassium > 5.5 meq/L, blood glucose > 15 mmol/L, serum creatinine >180 μmol/L), a copy of the laboratory data will be forwarded to the subjects' attending physician for potential follow-up. Based on the laboratory blood test results, eligible subjects will be asked to continue with the study protocol. In subjects who are ineligible for the study, no further involvement in the study will be required.

All study-related laboratory data will be forwarded to the data management centre (EPICORE Centre, University of Alberta) and the project office (Institute of Health Economics) for screening.

Blinding and Randomization

Eligible subjects will be randomized to either metformin or placebo tablets. To ensure blinding of subjects, investigators and outcome assessors, prior to the initiation of the study, the project office (i.e., Institute of Health Economics) will coordinate the prepackaging all study medication through the University of Alberta Hospital. A list of sequential study numbers will be assigned in a 1:1 ratio to either the metformin or placebo study group using a computer-generated block randomization sequence stratified by study site. Block randomization will ensure study groups are approximately of equal size throughout the enrollment period. A block size of four will be used and will not be disclosed to medical staff or the research coordinators. Randomization will be carried out through a secure website by EPICORE Centre.

Once group assignment for the sequential study numbers has been determined, for each sequential study number, two medication bottles will be prepared with either

placebo or metformin (500mg tablets; Apotex brand)) depending on the group assignment. Each medication bottle will contain a 3 month supply of the assigned study medication (i.e., 6 months total supply) and labeled with the appropriate study number.

Placebo tablets will be manufactured by Apotex to be identical in size, shape, and color as compared to the actual metformin tablets. All medication will subsequently be prepackaged in identical prescription bottles with identical labeling. All prepackaging of study medications will be completed by a licensed pharmacist in the University of Alberta pharmacy department. Thus, blinding of treatment assignment should be maintained throughout the study period.

Following the completion of the study and in accordance with the Consolidated Standards for Reporting of Trials (CONSORT) guidelines, the success of our blinding procedures will be evaluated by asking a series of questions to both the subject and research coordinators to evaluate which treatment they believed they had received (i.e., metformin or placebo). Subjects will subsequently be asked to indicate what led to the belief.

Baseline procedures

Subjects who provide informed written consent will be assigned the next sequential study number for the study site by the research coordinator. The research coordinator will then dispense the first 3 month medication supply bottle (metformin/placebo) to the subject according to the study number.

All subjects will receive the following information during the visit:

a) General information

The research coordinator will provide general education to subjects about heart failure and type 2 diabetes, including an overview of the diseases, the pharmacological and non-pharmacological treatment measures, and home monitoring. In addition, patients will receive written information regarding the above education. Subjects will also be provided with a contact number to call with any questions or concerns they may have.

b) Medication Information

The research coordinator will complete a detailed medication history with all subjects. Subjects will then be provided with information regarding their medications, outlining the reasons for use and proper administration. A Dosett™ will be provided to the subject to promote good adherence to their medications, with special emphasis on the study medication. A plan for missed doses and the development of adverse effects to the study medication will also be discussed with the subject.

To reduce the incidence of adverse effects to the study medication or placebo, subjects will be instructed to titrate their study medication dose. The dose of metformin or placebo will be titrated to the maximum dose of 1500mg/day over a 3 week period. Subjects will be initially instructed to take one 500mg tablet of metformin or one placebo tablet with their evening meal. After 1 week, a second 500mg metformin or placebo

tablet will be added to the breakfast meal (1000mg/day). After two weeks, the dose of metformin or placebo will be increased to the target dose of 1500mg/day through the addition of a 500mg metformin or placebo tablet at lunch. The metformin or placebo dose will be increased in this fashion unless side effects (e.g., gastrointestinal or hyper or hypoglycemic reactions) limit dose titration. A dose titration algorithm will be used to assess the patient for potential dose titration (Appendix C). In subjects with intolerable side effects, the dose of metformin or placebo will be reduced to the maximum tolerated dose of metformin or placebo. To ensure study medication is titrated appropriately, the research coordinator will also contact the subjects at 1 and 2 weeks to instruct subjects on the appropriate dosage changes. This dosage titration protocol is identical to the protocol utilized in the multi-centre metformin study.[1] A dose of 1500mg/day will be used, as this is a submaximal dose of metformin (i.e., maximal dose is 2550mg/day) and is unlikely to cause any serious adverse events when used either as monotherapy or in combination with other oral hyperglycemic agents.[1]

In addition, to be included in the study subjects must be willing to complete serum monitoring of blood glucose in the community. Research coordinators will ask subjects for the range of their blood sugars (i.e., either fasting or post-prandial) during all telephone and in-clinic visits. Subjects with self reported blood glucose levels less than 4 mmol/L or greater than 15 mmol/L or with signs and symptoms of hypoglycemia will be asked to see there local physician as a precautionary measure (Appendix C). The research coordinator will also contact the local physician to inform him/her of the subjects' blood glucose levels.

The research coordinator will also provide the subject with a medication calendar outlining the time and amount of dosage adjustment to be made to their study medication.

c) Clinical Event Diary

All subjects will be provided with a clinical event diary to record all clinical events. Specifically, subjects will be instructed to record all hospitalizations, emergency room visits, and unscheduled physician visits throughout the follow-up period.

d) Health-Care Provider Communication Letter

An information letter and a copy of the subject's consent to participate in the study will be forwarded by the research coordinator to the subject's family physician and community pharmacy. As part of the protocol, the subject's family physician will be unrestricted with respect to the treatment of the subjects' blood glucose levels. Antidiabetic medications may be modified by the family physician, however, no change in the subjects study medication or addition of metformin therapy will be permitted during the study period.

e) Six Minute Walk

All subjects will complete a six minute walk test to evaluate the impact of metformin therapy on functional capacity. The six minute walk test will be conduced at both the initial baseline visit and at the final 6 month evaluation.

f) Patient-Centered Outcomes

Patient centered outcomes will be assessed using generic and heart failure specific measures of health status. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item questionnaire that quantifies symptoms, physical limitations, social functioning, patients' self-efficacy, and quality of life. Scores range from 0-100 with higher scores representing better overall function. The KCCQ has been previously validated and has shown good reliability and responsiveness in heart failure patients.[41,42]

Generic health-related quality of life will be assessed using two measures, the RAND-12 and the EQ5D. The RAND-12 is an abbreviated version of the RAND-36 and is a commonly used health status profile measure.[43-46] The RAND-12 provides summary scores for a subject's physical and mental health status (i.e., physical component summary (PCS) and mental component summary (MCS)).[45] The EQ5D is composed of a preference based index score and a visual analog scale. Overall index scores range from -0.59 to 1.0, with -0.59 representing the utility of the worst possible EQ-5D health state, 0.0 representing dead and 1.0 representing perfect health.[47] The visual analog scale is a 20 cm scale with anchors of best imaginable health and worst imaginable health. The scale ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). Respondents are asked to rate their health on the VAS 'today'. The VAS provides an individual's preference, whereas the multi-attribute function provides a community preference.[47] The RAND-12 and EQ5D have been previously utilized in both patients with heart failure and diabetes and are considered to be valid and reliable measures in these populations.[41,42,48-50]

Patient centered outcomes will be assessed at baseline and at the 6 month follow-up through self-administered questionnaires.

Follow-up

During the 6 month community follow-up, subjects will be contacted by telephone at monthly intervals except for the third month and the final visit (i.e., 6 months), which will be completed in-person by the research coordinator (Appendix B). During these telephone calls, the research coordinator will reinforce the general and medication specific education to the patient. Subjects' blood glucose levels will be assessed and subjects will be evaluated for signs and symptoms of hypoglycemia. The research coordinator will also collect data on self-reported clinical events experienced by the patient since the last follow-up date. In situations where the reason for the clinical event is not known by the subject, the research coordinator will contact the family physician or hospital to acquire the necessary information or access the required information through the NetCare Databases.

Subjects will be asked to return to one of the heart function clinics for an in-person visit at 3 and 6 months (i.e., final visit). As with the telephone contacts, subjects will be

provided with education and ascertainment of clinical event data will be completed. In addition, laboratory blood work will also be completed.

Chemistry profiles will be collected at the 3 and 6 month in-person clinic visits. All results will be forwarded to the project office for screening and the data management center. The project office will screen all chemistry data for the presence of renal insufficiency as defined as a serum creatinine $\geq$ 225 umol/L. Although metformin therapy does not alter renal function, both heart failure and diabetes themselves increase the risk for the development of renal insufficiency. Furthermore, published literature indicates that subjects with renal insufficiency are at a higher risk for the development of lactic acidosis.[51,52] If renal insufficiency is identified, defined as a serum creatinine $\geq$ 225 umol/L. the research coordinator and local research physician will be notified. Since clinical events other than decreased renal function (e.g. dehydration, diuretics) can produce elevated creatinine levels in subjects with diabetes and heart failure, the diagnosis of renal insufficiency will be left to the discretion of the local research physician. The research coordinator will notify the project office of subjects subsequently identified as having renal insufficiency. Subjects' will be unblinded and removed from the study at the request of the local research physician or if the subject is diagnosed with lactic acidosis (either confirmed or probable).

In addition to chemistry profiles, an A1c will also be collected. The results will be forwarded to the project office and data management center. The results will not be available to the local research coordinator or medical staff to avoid potential unblinding through interpretation of the subjects laboratory values.

Subjects will be instructed to return their supply of study medication to the local research coordinator at the 3 and 6 month clinic visits. By returning the medication supply, an estimate of the subject's medication use behavior may be undertaken using a pill count. Subjects will not be informed that their adherence to the study medication is being assessed. Upon return of the study medication at the 3 month visit, the research coordinator will provide the subject with the next 3 month supply of study medication to the end of the 6 month study period.

During the clinic visits, the research coordinator will also conduct a medication history with the subject to determine if any medication regimens have changed since that last visit. Particular attention will be given to the subject's diabetes related medications. All subject self-reported diabetes medication regimens will be confirmed with the subject's community pharmacy.

Outcome Measures

Primary Outcome

The primary outcome of our study will be a combined endpoint of all-cause mortality or all-cause hospitalization. This outcome is considered to be the least biased approach when examining the overall efficacy and safety of a medication.[53]

Secondary Outcomes

Each component of the primary combined outcome will be analyzed separately. In addition, the mean change in A1c, six minute walk, and mean change in HRQL scores from baseline to the 6 month follow-up visit will also be assessed.

The safety of metformin will be assessed by the proportion of subjects developing lactic acidosis requiring urgent medical attention, as defined as an emergency room visit or hospitalization. All subjects with a probable diagnosis of lactic acidosis will be classified as having achieved the endpoint and will subsequently be unblinded by the project office and removed from the study.

Since the diagnosis of lactic acidosis is largely subjective, to verify the diagnosis, medical records of all subjects with a probably diagnosis of lactic acidosis will be reviewed retrospectively by the safety and efficacy monitoring committee. Lactic acidosis will be confirmed if both physicians confirm the diagnosis.

All laboratory data in the community will be completed by Dynacare Kasper Medical Laboratories (DKML) the Capital Health Region.

Sample Size Considerations

Data from a RCT we recently completed[27], in addition to observational data[4,16], indicates high event rates in subjects with diabetes and heart failure with a previous hospitalization in the community setting. Our RCT data, which is the most conservative estimate, indicates 56 and 69 percent of subjects with heart failure and diabetes will die or be hospitalized within 6 months and 1 year, respectively, following hospital discharge. Thus to detect an absolute difference in event rates of 10% (i.e., 55% versus 45%) in our primary outcome with a two-tailed alpha = 0.05 and beta = 0.20, we estimate that we would need 400 subjects per study arm. That is, a total sample size of 800 subjects. The estimated sample size will be increased by a further 25%, to account for losses to follow-up, drop-outs, and provide additional power for the assessment of secondary outcomes. Thus, our final total sample size to be enrolled in the RCT will be 1000 subjects.
Note: Approximately 100 subjects, which represents 10% of the anticipated number of subjects required for a full RCT, will be included in the pilot study to assess the feasibility of conducting the full RCT.

Data Analysis

All statistical analysis will be performed using SPSS for Windows (version 14.0). An a priori probability of committing a type 1 error (i.e., alpha level) of 0.05 will be applied for all tests of statistical significance. All analyses will be conducted from an intention to treat perspective. The data analyst will be blinded to treatment assignment. This will be completed by using a dummy variable assigned by the data management center to represent group assignment.

For individuals who die, are withdrawn from the study, or are lost to follow-up, the last observation carried forward will be used to provide complete data for assessment of the primary outcome. This technique will provide a conservative approach for handling the missing data in the analysis.

The primary outcome (all-cause mortality and hospitalization), secondary outcomes for the individual components, and risk of the development of lactic acidosis will be

assessed using relative risk (RR) calculations. For example, from a typical 2 x 2 table the RR for the combined endpoint will be calculated as follows:

$$RR = \frac{a/n_{(metformin)}}{c/n_{(placebo)}}$$

where
a = observed frequency of the combined endpoint in the metformin group
c = observed frequency of the combined endpoint in the placebo group
$n_{(metformin)}$ = total number of subjects in the metformin group
$n_{(placebo)}$ = total number of subjects in the placebo group

Confidence intervals (CI) will be calculated for the RR estimates. By convention, 95% confidence intervals will be calculated using the following test-based method (Hennekens & Buring 1987):

$$95\%\ CI = RR^{(1 \pm 1.96/\chi)}$$

where χ is the square root of the chi-square statistic (χ^2). χ^2 values will be calculated using the formula and notations from the typical two-by-two table (Hennekens & Buring 1987):

$$\chi^2 = \frac{(ad - bc)^2(T)}{(a+b)(c+d)(a+c)(b+d)}$$

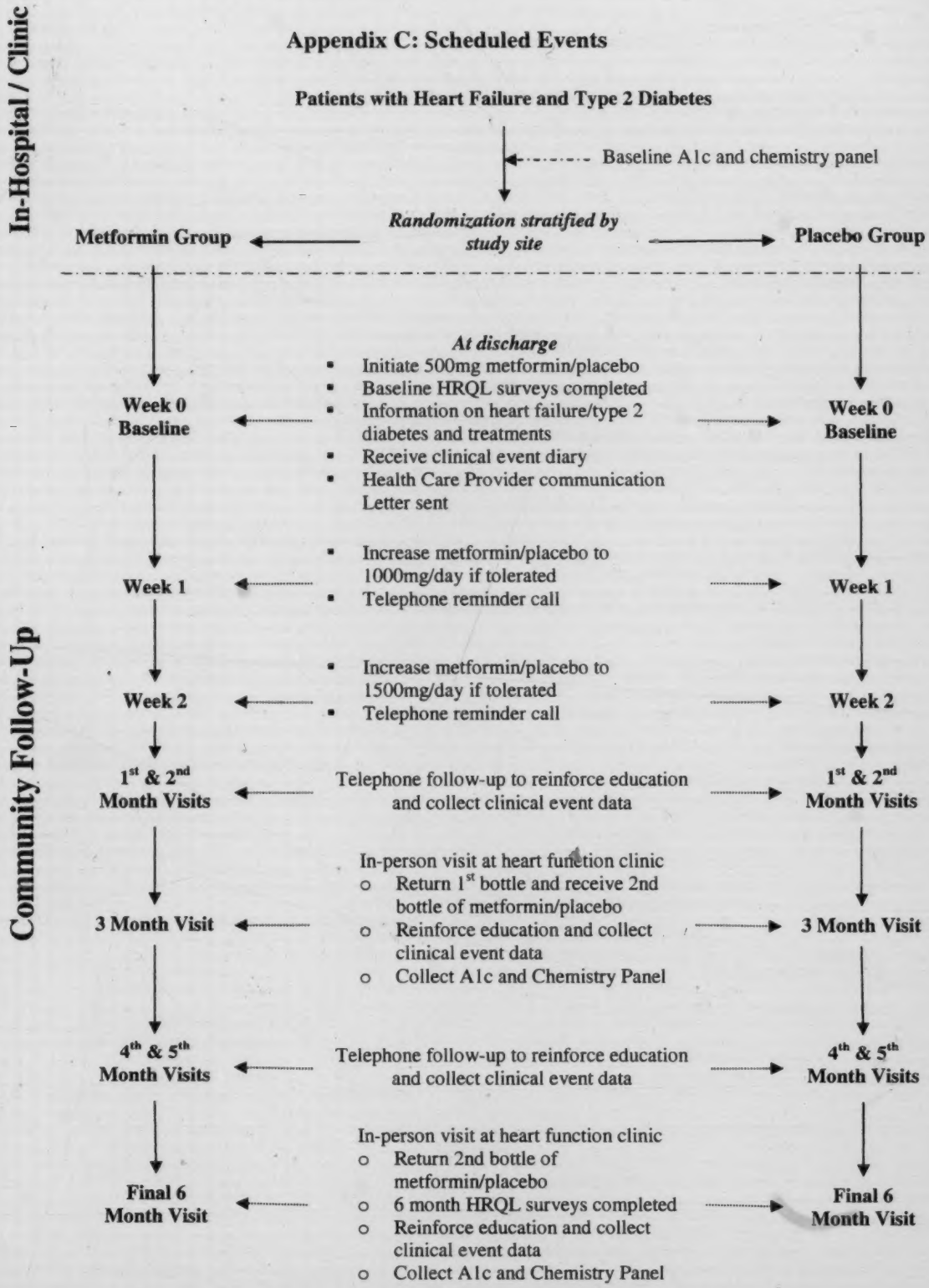
The secondary outcomes of change in A1c and change in HRQL scores from baseline to 6 months will be assessed using analysis of variance. In addition, although not a specific endpoint of the study, change in A1c from baseline to 3 months will also be assessed using analysis of variance. This analysis will provide information on the efficacy and safety of metformin therapy throughout the follow-up period.

Safety and Efficacy Monitoring Committee

An independent safety and efficacy monitoring committee will be composed of two physicians and a biostatistician. The committee will be blinded to treatment allocation. As indicated previously, the medical records of all subjects with a probably diagnosis of lactic acidosis will be reviewed retrospectively by the safety and efficacy monitoring committee. Lactic acidosis will be confirmed if both physicians confirm the diagnosis.

In addition, the safety and efficacy monitoring committee will complete an interim analysis after 50 subjects have been followed for 3 months. Treatment groups will be compared with respect to the combined endpoint and development of lactic acidosis. The trial will be stopped if the metformin group is observed to have a statistically significant higher incidence of either the combined endpoint or the development of lactic acidosis. No data will be released unless this is achieved.

Appendix C: Scheduled Events


In-Hospital / Clinic
Community Follow-Up
Patients with Heart Failure and Type 2 Diabetes
Baseline A1c and chemistry panel
Randomization stratified by study site
Metformin Group
Placebo Group
At discharge
Initiate 500mg metformin/placebo
Baseline HRQL surveys completed
Information on heart failure/type 2 diabetes and treatments
Receive clinical event diary
Health Care Provider communication Letter sent
Week 0 Baseline
Week 0 Baseline
Increase metformin/placebo to 1000mg/day if tolerated
Telephone reminder call
Week 1
Week 1
Increase metformin/placebo to 1500mg/day if tolerated
Telephone reminder call
Week 2
Week 2
1st & 2nd Month Visits
Telephone follow-up to reinforce education and collect clinical event data
1st & 2nd Month Visits
In-person visit at heart function clinic
Return 1st bottle and receive 2nd bottle of metformin/placebo
Reinforce education and collect clinical event data
Collect A1c and Chemistry Panel
3 Month Visit
3 Month Visit
4th & 5th Month Visits
Telephone follow-up to reinforce education and collect clinical event data
4th & 5th Month Visits
In-person visit at heart function clinic
Return 2nd bottle of metformin/placebo
6 month HRQL surveys completed
Reinforce education and collect clinical event data
Collect A1c and Chemistry Panel
Final 6 Month Visit
Final 6 Month Visit

Appendix D: Metformin/Placebo Dosage Adjustment Decision Guide

Self-monitored FPG Average Measurements from 2 preceding days	Metformin/Placebo Dosage Adjustment
>15 mmol/L	**Increase dose by 500mg (max 1500mg/day) and Contact MD**
10-15 mmol/L	**Increase dose by 500mg (max 1500mg/day)**
>4 mmol/L and <10 mmol/L	**No dosage adjustment**
Any reading ≤ 4.0 mmol/L or severe hypoglycemia	**Decrease Dose by 250mg and Contact MD***

** if low reading/hypoglycemia occurs during daytime, decrease morning dose by 250mg; If low reading/hypoglycemia occurs during evening or night time, decrease supper dose by 250mg*

Note - If patient has any intolerable side effects, maintain current dose (or decrease dose by 250mg if patient indicates side effects are severe) and reassess possibility of dosage increase on next contact.

CHAPTER 5: BIAS RELATED TO THE USE OF COMPOSITE OUTCOMES: PROBLEMS AND SOLUTIONS THAT INCORPORATE QUALITY OF LIFE ADJUSTED SURVIVAL ANALYSES

5.1 Abstract

Background: Composite outcomes typically assume equal weighting of each component equally. In many cases, however, these components represent potentially competing events (e.g., reduced death vs. increased hospitalization) and might lead to over- or under-estimates of true benefit. We used health-related quality of life (HRQL) weights to "quality-adjust" survival analyses and improve the clarity of reporting composite event outcome differences.

Methods: The commonly used composite outcome of mortality or hospitalization in patients with heart failure was evaluated using data from two published studies of heart failure patients: an observational study with 2.3 years follow-up comparing outcomes in users of metformin (n=208) vs. users of sulfonylurea (n=773) and a randomized trial with 3.1 years follow-up comparing digoxin (n=3397) vs. placebo (n=3403). For each study, we partitioned the composite outcome into its component health states and assigned literature-derived utilities: H_1 (initial health state, 0.81); H_2 (state after hospitalization until death or censoring, 0.57), H_3 (dead, 0). Total quality-adjusted survival (QAS) time was calculated by summing the product of mean survival time for each health state and its assigned utility. Ninety-five percent confidence intervals (95%CI) were generated through bootstrapping procedures.

Results: In the first study, metformin users exhibited a reduction in the composite outcome [658 (85%) compared to sulfonylurea users 160 (77%); HR 0.83 (95%CI 0.70-0.99)] and an apparent survival advantage of 0.75 years. However, the QAS time was only 0.50 years (95%CI 0.48-0.52). For the second study, digoxin was associated with a reduction in the composite outcomes [1291 (38%)] compared to placebo [1041 (31%)]; HR 0.75 (95% CI 0.69-0.82) and a gain of 0.06 years; however, the QAS time was 0.11 years (95%CI 0.106-0.114). In sensitivity analyses, results varied substantially depending on the choice of utility weights but in all cases standard methods substantially

over-estimated (in the metformin example) or under-estimated (in the digoxin example) the benefits of these medications.

Conclusion: Studies using unweighted composite endpoints may potentially over- or under-estimate treatment benefits. Incorporating patient-reported HRQL to adjust for unequal health states in composite outcomes yields more accurate estimates of treatment effect.

5.2 Introduction

Composite outcomes are commonly used in randomized controlled trials and epidemiological research, especially in cardiovascular disease. There are many advantages to using composite outcomes, namely increased event rates and improved statistical power and overall efficiency of the study. However, several concerns exist with the use of composite outcomes, in particular, difficulties in interpretation of results when the individual components of the composite outcome carry vastly different implications for patients and may be associated with competing levels of risk.[1] For example, the composite outcome of all-cause mortality or hospitalization is often used in studies of heart failure. Depending on the rates of individual events, one can envision difficulties in comparing the effects of two treatments if Treatment A reduced mortality but increased all-cause hospitalizations while Treatment B had no effect on mortality but reduced all-cause hospitalizations.

The problem to date has been that most composite outcomes have been based on the assumption that each component of the outcome (i.e., each health state) is equally important. Although there are certainly cases where this assumption is valid, it is more likely that each component of a composite outcome would impact a patient's overall quality of life differently. One approach to address this situation is to account for potential differences in health states by assigning unequal weights to the components of the composite outcome, although the weights assigned are usually based on 'expert opinion'.[2-5] Since it is ultimately the patient that will experience the events in question, it would seem more reasonable to incorporate the patient's perspective when adjusting for unequal outcomes in clinical research.

An alternative method for assigning weights that incorporates the patient's perspective is the use of health related quality of life (HRQL). HRQL measures are increasingly used in clinical trials, even serving as the primary outcome for many trials.[6,7] By incorporating HRQL into survival analyses, index measures could be used to adjust for the unequal impact of health states used in composite outcomes, thereby providing a 'weighted' outcome assessment to incorporate different degrees of quality and quantity of life.[8] Furthermore, incorporation of HRQL into survival analysis would align clinical research with recommended methods for economic evaluations[9], providing better

estimates of the true impact of health care interventions. The concept of using HRQL to adjust survival analyses for different health outcomes has been used extensively in the area of oncology, where many treatments do not provide substantial survival advantage.[8] This technique has not, to our knowledge, been similarly employed in cardiovascular research, specifically among patients with heart failure. In this paper, we illustrate how HRQL can be incorporated into survival analysis of commonly used composite outcomes in observational studies and clinical trials to provide a quality adjusted survival (QAS) analysis. [10]

5.3 Methods

Overview

We illustrate the use of a QAS analysis using Cox proportional hazards models as originally proposed by Cole et al.[10] We modified and applied the technique to the commonly reported composite outcome of mortality or hospitalization. To illustrate the versatility of the method we applied it to two previously published studies, an observational study evaluating the use of different oral antidiabetic agents in heart failure and a randomized controlled trial comparing digoxin against placebo in patients with heart failure.[11,12] Institutional Review Board approval was granted for the both studies by the University of Alberta; data for the Digitalis Investigation Group (DIG) study is public domain and was obtained from the National Heart, Lung and Blood Institute (NHLBI).

Data Sources

i. Metformin Use in Heart Failure

The data sources and population studied were previously described in detail.[11] Briefly, between January 1, 1991 and December 31, 1999, 1,833 eligible subjects newly treated with oral antidiabetic agents and incident heart failure were identified using the administrative databases of Saskatchewan Health. Subjects were categorized into three mutually exclusive groups according to oral antidiabetic prescription claims: 773 (42%) were treated with sulfonylurea therapy alone, 208 (11%) with metformin alone, and 852 (47%) were treated with combinations of sulfonylurea and metformin. For the illustrative

purposes of this study, only individuals who received either metformin or sulfonylurea monotherapy were included. All subjects were prospectively followed until death, termination of Saskatchewan Health coverage, or December 31, 1999, providing a maximum follow-up of 9 years.

Using standard Cox proportional hazards regression techniques, after adjustment for potentially confounding variables (i.e., age; sex; a modified Chronic Disease Score (CDS)[13,14]; therapies known to affect heart failure outcomes: ACE inhibitors, angiotensin II blockers, beta-blockers, antiplatelet agents, nitrates, lipid-lowering therapies, antiarrhythmic agents, and spironolactone; and total physician visits prior to heart failure diagnosis), a reduction in events in favor of the metformin group compared to sulfonylurea therapy was observed for both all-cause mortality [69 (33%) vs. 404 (52%); hazards ratio (HR) 0.70 (95% CI 0.54-0.91)] and the composite outcome of "all-cause death or all-cause hospitalization" [160 (77%) vs. 658 (85%); HR 0.83 (95% CI 0.70-0.99)].[11]

ii. The DIG Study

The rationale, design, and results of the DIG study has been previously described in detail.[12,15] A total of 6800 patients with heart failure and a left ventricular ejection fraction ≤0.45 percent were randomly assigned to receive either digoxin or placebo. After an average follow-up of 37 months, there was no difference between the study groups with respect to the primary outcome of all-cause mortality [1194 (35%) in placebo group versus 1181 (35%) in digoxin group; relative risk (RR) 0.99 (95% CI 0.91-1.07)]. There was a trend toward a lower risk of heart failure related mortality in the digoxin group compared to the placebo group [394 (12%) vs. 449 (13%); RR 0.88 (95% CI 0.77-1.01)]. In addition, the risk associated with the composite outcome of death due to worsening heart failure or hospitalization related to that diagnosis was lower in the digoxin group [1041 (31%) in digoxin group vs. 1291 (38%) in placebo group; RR 0.75 (95% CI 0.69-0.82)].[12]

Weighted Composite Outcome

We applied the technique to the all-cause mortality or hospitalization composite outcome in the metformin study and to the heart failure-specific mortality or hospitalization composite outcome in the DIG study. For each study, the transitional survival function (i.e., survival curves) for the mortality component of the composite outcome was first calculated. The transitional survival function for the composite outcome was then computed for each study. Since the area under the survival curves represents an estimate of the mean survival time associated with that outcome, the mean duration of each health state can be calculated for the successive transition times.[10] That is, the composite outcome can be partitioned into its component health states (i.e., death and hospitalization) by subtracting the composite outcome survival curve from the overall mortality survival curve, providing a transition time for each of its component functions.[8,10]

In these two examples, we considered three potential successive health states patients may transition through during the periods of the study: 1) state H_1 was the initial health state of the patient and represents the state of health prior to a hospitalization, death or censoring at the end of follow-up if no hospitalization has occurred (i.e., the mean survival time associated with the area under the composite outcome curve); 2) state H_2 was the health state of the patient after a hospitalization until either death or censoring at the end of follow-up (i.e., the mean survival time associated with the area between the composite outcome survival curve and the mortality curve); 3) state H_3 was the health state dead (no time is associated with this health state).

Each health state was associated with a different HRQL, represented by a utility coefficient.[10] For these analyses, we applied utility coefficients from the literature. For state H_1, the utility coefficient was set at 0.81, based on HUI3 scores observed for subjects with heart disease and diabetes in the Canadian population,[16,17] and is similar to utility weights observed in patients with heart failure alone.[16,17] In patients with heart failure, a hospitalization is associated with a 30% reduction in the patients HRQL[17] resulting in a utility coefficient of 0.57 for state H_2. By convention, the health state dead (H_3) was assigned a utility score of zero.[16]

Analysis

For the metformin study, the transitional survival functions for each health state (i.e., all-cause death or all-cause hospitalization) for the metformin and sulfonylurea groups were estimated using Cox proportional hazards models after adjustment for the confounding covariates.[10] The survival functions for the treatment groups for the health states were estimated at the mean values of the confounding covariates, although any hypothetical combination of covariate values could have been used.

For the DIG study, there were no significant differences between the baseline characteristics between the digoxin and placebo patients due to the randomized design.[12] As a result, the transitional survival functions for each health state (i.e., heart failure related death or hospitalization) for the digoxin and placebo group were estimated using Cox proportional hazards models with no adjustment for confounding covariates.

For each health state, the mean time spent in the health state was calculated by integrating the estimated survival function from zero to the upper limit of observation for the treatment groups, 7.8 years and 4.9 years for the metformin study and DIG study, respectively. Time in state H_1 was simply the integrated survival time for the composite outcome survival curve. Time in state H_2 was calculated by integrating the mortality curve (overall survival time) and subtracting the mean time spent in state H_1. Quality adjusted time in each health state was then calculated by multiplying the mean time spent in each health state by the respective utility coefficient.[10] Summation of these quality adjusted times provided an estimate of the overall quality adjusted survival during the study period for each treatment group.

To generate estimates of standard error of the mean quality adjusted survival estimates for the treatment groups, we bootstrapped the procedure 500 times for the metformin study and 1000 times for the DIG study. The studies were bootstrapped differently due to the difference in the number of observations within each study. Previous research has shown that mean quality adjusted survival estimates are asymptotically normally distributed.[10,18] As a result, the difference in mean quality adjusted survival between the treatment groups were compared using a Students' t-test.

Sensitivity Analysis

Sensitivity analyses were used to evaluate the effect of different utility coefficients for the health states on the results for both the metformin and DIG study. The utility weights for health states H_1 and H_2 were varied by increasing or decreasing the utility coefficients by 0.03, which is considered a clinically important difference on the HUI3.([19]). All analyses were conducted using SAS for windows 9.1, Cary, NC, USA.

5.4 Results

i. Metformin use in Heart Failure

The mean age of our study cohort was 74 (SD 10) years, 59% were male, and mean follow-up was 2.3 (SD 1.9) years following the diagnosis of heart failure. The sulfonylurea group was slightly older, had less comorbidity, and had fewer prescription claims for heart failure-related medications compared to the metformin monotherapy group (Table 5.1).

After partitioning the survival functions, integration of the all-cause mortality survival function resulted in a total survival time of 4.64 for sulfonylurea users and 5.39 years for metformin users; for the composite outcome curves, mean survival time in health state H_1 was 1.32 for sulfonylurea users and 1.65 years for metformin users (Figure 5.1a and b) and mean time in health state H_2 was 3.33 and 3.74 years for sulfonylurea users and metformin users, respectively (Table 5.2).

Using traditional survival analysis, which assumes that those who have not yet died are in perfect health (i.e., utility equal to 1 for all health states) until the time of death, and weights the time before and after hospitalization equally, sulfonylurea users would have an expected total adjusted survival of 4.64 years and the metformin users would have an expected adjusted survival of 5.39 years in this dataset. This could be interpreted as a gain of 0.75 life years associated with metformin use compared to sulfonylurea use in this cohort, which represents the difference in mean time until death for the two groups. However, sulfonylurea users spent a mean time of 1.32 years in health state H_1 at an expected utility of 0.81 and 3.33 years at an expected utility of 0.57 for health state H_2, for a total quality adjusted survival time of 2.97 years. Conversely, the metformin users spent a mean time of 1.65 years in health state H_1 and 3.74 years in

health state H_2, for a total quality adjusted survival of 3.47 years (Table 5.2). As a result, metformin users exhibited a net increase of 0.50 QALYs as compared to the sulfonylurea therapy users, which is statistically significant based on a standard error of the difference of 0.00743 estimated from the bootstrap procedure (95% CI (0.48 – 0.52), $p<0.001$). Furthermore, this estimate is 33% lower than the result generated by standard survival analysis, which was based on the assumptions of perfect health until death occurred and equal weighting of time before and after hospitalization for those who were hospitalized. Thus, in this case, traditional methods led to a 50% over-estimate of potential benefits related to treatment of diabetic heart failure patients with metformin.

ii. DIG Study

The mean age of the DIG study participants was 63 (SD 11) years, 78% were male, and mean follow-up was 37 (range 28 to 58) months following randomization. There were no significant differences between the baseline characteristics between the digoxin or placebo patients (Table 5.3).[12] Mean survival times were 4.31 for the placebo group and 4.37 years for the digoxin group; for the composite outcome curves, estimated total event-free survival time was 3.22 years for the placebo group and 3.51 years for the digoxin group (Figure 5.2a and b).(Table 5.4). Assuming perfect health, digoxin users had an apparent net survival benefit of 0.06 years compared to placebo. However, the placebo users spent a total time of 3.22 years in health state H_1 at an expected utility of 0.81 and 1.09 years at an expected utility of 0.57 for health state H_2 resulting in a total quality adjusted survival of 3.22 years. Conversely, the digoxin group spent a total time of 3.51 years in health state H_1 and 0.86 years in health state H_2 resulting in a total quality adjusted survival of 3.33 years. Therefore, after taking into account the greater time spent before hospitalization in the digoxin group, the digoxin group had net gain of 0.11 QALYs compared to the placebo group, which is statistically significant based on a standard error of the difference of 0.002 estimated from the bootstrap procedure (95% CI (0.106-0.114), $p<0.001$). Furthermore, this estimate is 42% higher than the standard survival estimate based on equally weighted outcomes. Thus, in this case, traditional methods led to an under-estimate of potential benefits related to treatment of heart failure patients with digoxin.

Sensitivity analyses

In the analyses described above, we applied deterministic utility coefficients to our health states taken from the literature. Therefore, we conducted a sensitivity analysis to assess the effect of varying the utility coefficients by a clinically important difference (0.03) on the QALY estimates for health state H_1 and H_2 for the metformin and DIG study (Tables 5.5a and b). Variations in the utility coefficients resulted in changes to both the individual QALYs calculated for each health state and consequently to the differences between study groups. All sensitivity analyses confirmed that the standard survival estimates over-estimated benefits by 43% to 57% for the observational metformin study and under-estimated benefits of digoxin by 32% to 50% in the DIG study.

5.5 Discussion

We have demonstrated a method that quality-adjusts survival to deal with the potentially unequal impact of the individual components of composite outcomes used in observational studies and randomized controlled trials. By incorporating an estimate of the impact on patients HRQL into the analysis, a weighted composite outcome may provide a more 'valid' representation of the true benefits or harm associated with a therapy. In the two examples illustrated in this study, incorporation of HRQL into the survival analyses resulted in quality adjusted survival estimates which were 33% lower in the metformin study and 83% higher in the DIG study compared to the original estimates based on the assumption that the health states comprising the composite outcome are equally weighted. It is clear that without using methods such as ours, treatment effects based on composite outcomes (at least in studies of heart failure) may be biased, and the direction of bias is not necessarily predictable.

Composite outcomes are used frequently in observational studies and randomized controlled trials. However, the implicit assumption of each component being of equal importance to patients, providers, and payers, seems untenable. For example, in a recent large randomized controlled trial of an antidiabetic therapy, an equally weighted composite outcome consisting of all-cause mortality, nonfatal myocardial infarction, acute coronary syndrome, cardiac intervention (coronary artery bypass graft or

percutaneous coronary intervention), stroke, leg amputation, bypass surgery or leg revascularization was evaluated.[19] Since the components were equally weighted, if one person had a leg revascularization and another a non-fatal stroke, they were both considered as having achieved the composite outcome. Clearly, however, a stroke has a significantly larger impact on a patient's health related quality of life following the event compared to a leg revascularization. Further, any non-fatal event is considered of equal importance to death. By incorporating these differences into the composite outcome, it is possible that the outcomes evaluated may be more sensitive to treatment effects and indeed, more sensible.

A recent systematic review and meta-analysis of cardiovascular-related randomized controlled trials also suggested that the components of composite outcomes often have substantially different impacts on patients' health and using implicitly equal weights may lead to biased conclusions[5] Like our examples, the authors reassigned unequal weights to components of various composite outcomes in their meta-analysis, suggesting that equally weighted composite outcomes lead to an overestimate of treatment effects.[5] Our results suggest that, in fact, the bias may go in either direction, depending on the outcomes assessed. Furthermore, while the authors used their own 'expert opinion' to derive weights,[5] we believe patient-reported HRQL provides a more valid assessment of how important various outcomes are to patients themselves.

Importantly, however, the validity of the quality adjusted estimate depends largely on the utility weights assigned to the health states of the component outcome. As shown in our sensitivity analyses, changes in the utility weights assigned to each health state can have an important effect on the quality adjusted survival estimates. As a result, care must be used in assigning the utility weights to the health states. In the setting of randomized controlled trials, prospectively collecting the utility estimates by incorporating preference-based index measure at appropriately timed intervals throughout the trial would be ideal. Although each trial will be different, minimally a baseline utility estimate and an estimate which is timed closely to important events would be required. In observational studies where prospective collection of utility estimates is not possible, carefully selected literature-based estimates may be used and documented. Ideally, these estimates should be from patients with similar characteristics, cultural values, and

outcomes as those being evaluated in the observational study. Alternatively, for both observational studies and clinical trials, threshold utility analyses can be performed for unknown utility estimates.[8,10]

In studies where economic evaluations are being considered, the use of quality-adjusted survival would be even more advantageous. Although often overlooked, results from most survival analyses evaluating composite outcomes are not easily amenable to economic evaluations. Economic evaluations often incorporate QALYs into their analysis (e.g., cost utility analysis) to guide decisions regarding the economic viability of health care interventions by evaluating the cost per QALY gained associated with the treatment. Indeed, economic analyses based on equally weighted components of composite outcomes may over- or under-estimate the true economic impact of the health care intervention.

As an example, for the DIG study, imagine that the direct health care costs associated with using digoxin therapy is $5,000 per year more compared to not using digoxin. Assuming each health state is of equal importance and is associated with a utility of 0.81 (the initial state H_1 utility value), digoxin use would have resulted in a net gain of 0.05 QALYs (net increase in survival of 0.06 years for digoxin therapy multiplied by the utility value of 0.81). This would have resulted in an incremental cost-utility ratio of $100,000 per QALY gained ($5,000/0.05 QALYs) for digoxin therapy, which may be considered 'unacceptable' by today's standards.[20] However, using quality adjusted survival resulted in a net increase of 0.11 QALYs for digoxin therapy. This would result in a more favorable incremental cost utility ratio of $48,454 per QALY gained.

Although there are several advantages to using QAS analyses, there are also other important considerations. First, the quality adjusted survival estimate using the methods we described is restricted to the upper limit of follow-up in the study. As a result, this method provides no information on the 'lifetime' estimates associated with the therapy. Second, we used the simplest presentation of this method, which assumes a progressive health state model, where hospitalization preceded death. Although this is appropriate for many disease conditions, it may not be suitable for all. Parametric methods have been developed, however, that overcome the limitations of restricted follow-up time and the need for progressive health state models.[21] In addition, this model may be extended to

account for repeated failure times and the use of time-varying covariates.[10] Third, all assumptions associated with Cox proportional hazards regression also apply to this method, including constant hazards over time and the concern for misleading results in the presence of competing risks.[22] In the DIG study, for example, we evaluated the risk associated with the composite outcome of death due to worsening heart failure or hospitalization related to that diagnosis. For illustrative purposes, we chose this composite outcome as it was one of the main previously published composite outcomes of the DIG trial. Importantly, however, due to the cause-specific nature of the outcome, it may be susceptible to competing risks. As a result, it is important to consider the potential impact of competing risk in all Cox proportional hazards models, regardless of its application in quality adjusted survival. Finally, our examples were restricted to one type of composite outcome evaluated for only one common condition.

Thoughtful and well-constructed composite outcomes are important in observational studies and clinical trials, but traditional methods of analysis may lead to biased estimates of treatment benefit. By incorporating patient-reported HRQL into survival analyses as outlined in our study, the potential impact of the individual components of the composite outcome on the patient's health can be assessed more directly; therefore, the potential benefits, harms, or costs associated with therapy may be more transparent to patients, providers, and policy-makers.

Disclaimer

This study is based on non-identifiable data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

The Digitalis Investigation Group (DIG) is conducted and supported by the NHLBI in collaboration with the DIG Study Investigators. This Manuscript was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the DIG study or the NHLBI.

Table 5.1. Study Cohort Characteristics for Metformin Use in Heart Failure

Characteristic	Sulfonylurea Monotherapy (n = 773)	Metformin Monotherapy (n = 208)	P Value*
	No. (%) or Mean ± SD		
Age – yrs	74.8 ± 10.1	72.5 ± 10.6	<0.001
Sex – male	451 (58)	123 (59)	0.40
Duration of Follow Up after diagnosis of heart failure (yrs)	2.3 ± 2.0	2.3 ± 1.8	<0.001
Chronic Disease Score	10.7 ± 3.7	11.6 ± 3.6	<0.001
Median	10.0	11.0	
Total Physician Visits†	41.6 ± 44.5	48.0 ± 40.0	<0.001
Myocardial Infarction	72 (9)	20 (10)	0.645
Ischemic Heart Disease	152 (16)	32 (15)	0.874
Cerebrovascular Disease	88 (11)	19 (9)	0.490
Other Diseases of Arteries, Arterioles and Capillaries	27 (4)	6 (3)	0.91
Medications‡			
Thiazide Diuretics	214 (28)	59 (11)	0.36
Loop Diuretics	595 (77)	157 (76)	0.061
ACE Inhibitors	476 (62)	148 (71)	<0.001
ARBs	38 (5)	17 (8)	0.008
Antiplatelet Therapy	300 (39)	92 (44)	0.24
Antiarrhythmic Agent	369 (48)	109 (52)	0.45
Beta Blockers	251 (33)	90 (43)	<0.001
Spironolactone	113 (15)	29 (14)	0.77
Lipid Therapy	123 (16)	49 (24)	<0.001
Nitroglycerin	357 (46)	106 (51)	0.04

* omnibus p-values from χ^2 test or ANOVA

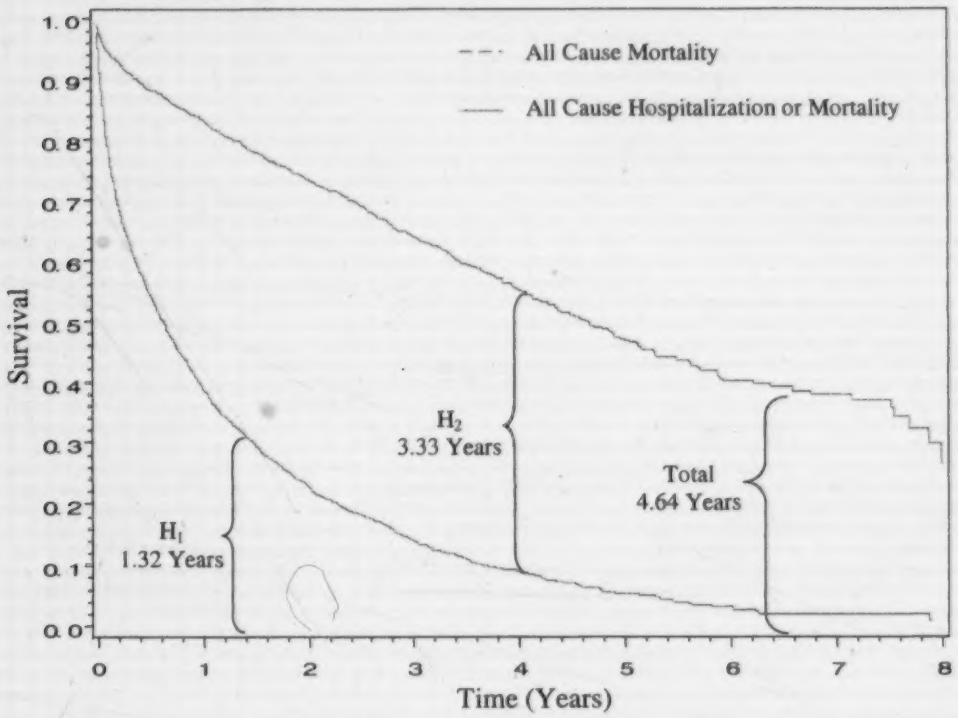
† total physician visits prior to HF diagnosis

Table 5.2. Integrated Survival Time for Sulfonylurea and Metformin Groups per Health State

Group	Survival in H_1 (Years)	Survival in H_2 (Years)	Total Survival (Years)	Quality Adjusted Survival (QALY)
Sulfonylurea	1.32	3.33	4.64	2.97
Metformin	1.65	3.74	5.39	3.47

Figure 5.1. Partitioned Survival Functions for All-Cause Mortality and All-Cause Hospitalization.

A. Sulfonylurea Therapy



B. Metformin Group

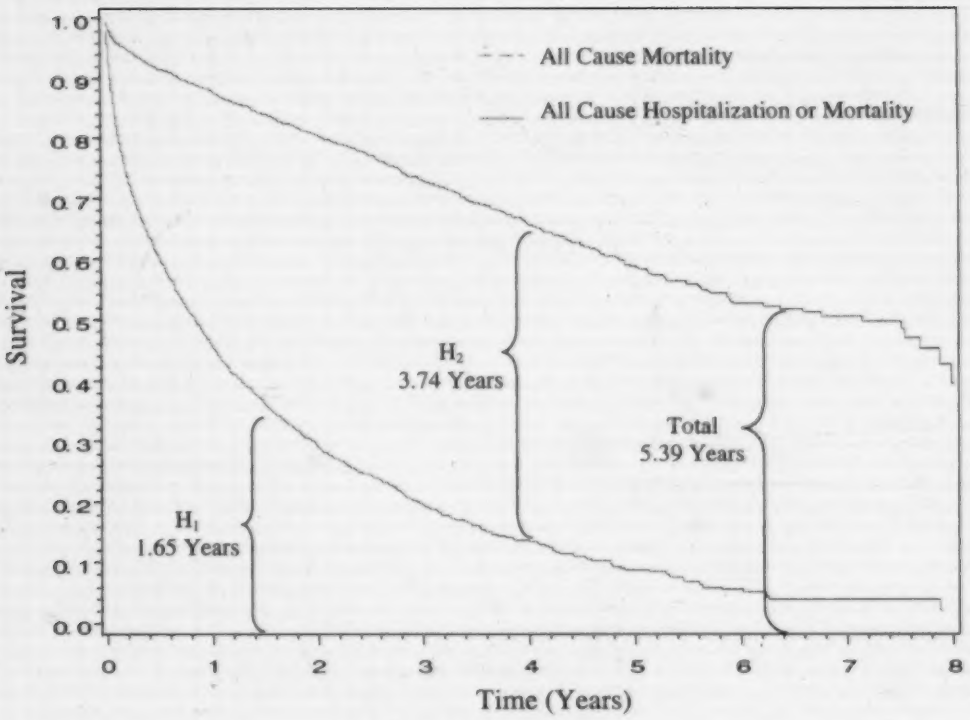


Table 5.3. Selected Study Characteristics for DIG Trial

Characteristic	Placebo Group (n = 3403)	Digoxin Group (n = 3397)	P Value*
	No. (%) or Mean ± SD		
Age – yrs	63.5 ± 10.8	63.4 ± 11.0	0.63
Sex (male)	2639 (78)	2642 (78)	0.82
Nonwhite Race	504 14.8	487 (14.3)	0.58
Ejection Fraction (%)	28.4 ± 8.9	28.6 ± 8.9	0.38
Duration of heart failure (mo)	29.8 ± 36.5	30.5 ± 37.2	0.42
NYHA Class			
I	442 (13)	465 (14)	
II	1854 (55)	1810 (53)	0.61
III	1039 (31)	1042 (31)	
IV	66 (2)	76 (2)	
Medical history			
Previous myocardial infarction	2221 (65)	2198 (65)	0.64
Current angina	899 (26)	922 (27)	0.50
Diabetes	972 (29)	961 (28)	0.80
Hypertension	1557 (46)	1527 (45)	0.51
Primary cause of heart failure			
Ischemic	2398 (71)	2405 (71)	0.77
Nonischemic	1005 (29)	992 (29)	
Medications			
Diuretics	2797 (82)	2759 (81)	0.30
ACE Inhibitors	3225 (95)	3197 (94)	0.24
Nitrates	1466 (43)	1432 (42)	0.44
Hydralazine	64 (2)	22 (2)	0.26

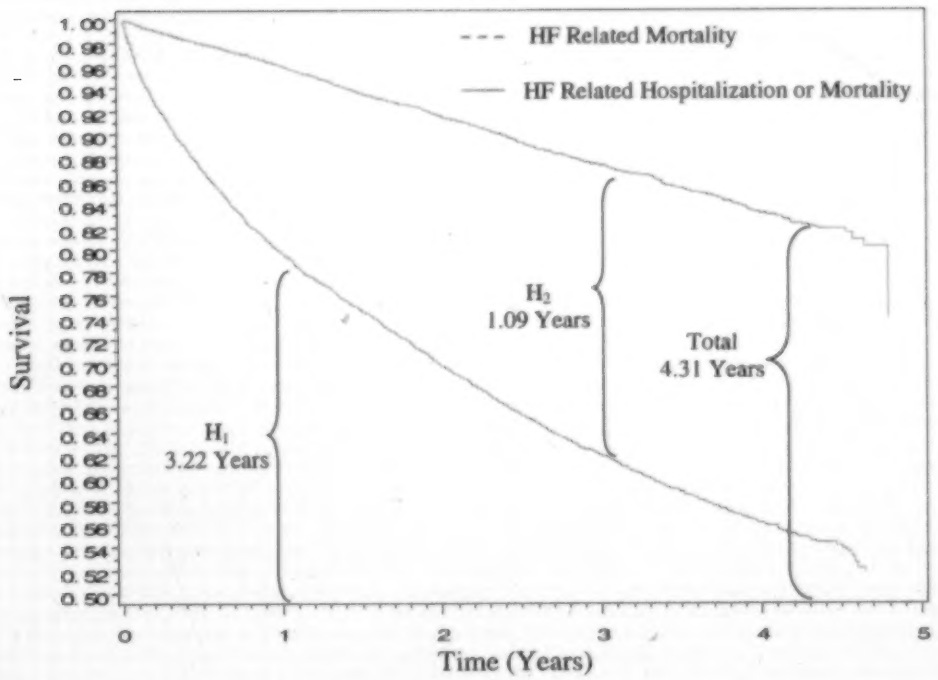
* omnibus p-values from χ^2 test or ANOVA

Table 5.4. Integrated Survival Time for Placebo and Digoxin Groups per Health State

Group	Survival in H_1 (Years)	Survival in H_2 (Years)	Total Survival (Years)	Quality Adjusted Survival (QALY)
Placebo	3.22	1.09	4.31	3.23
Digoxin	3.51	0.86	4.37	3.33

Figure 5.2. Partitioned Survival Functions for Death due to Worsening Heart Failure or Hospitalization Related to that Diagnosis.

A. Placebo Group



B. Digoxin Group

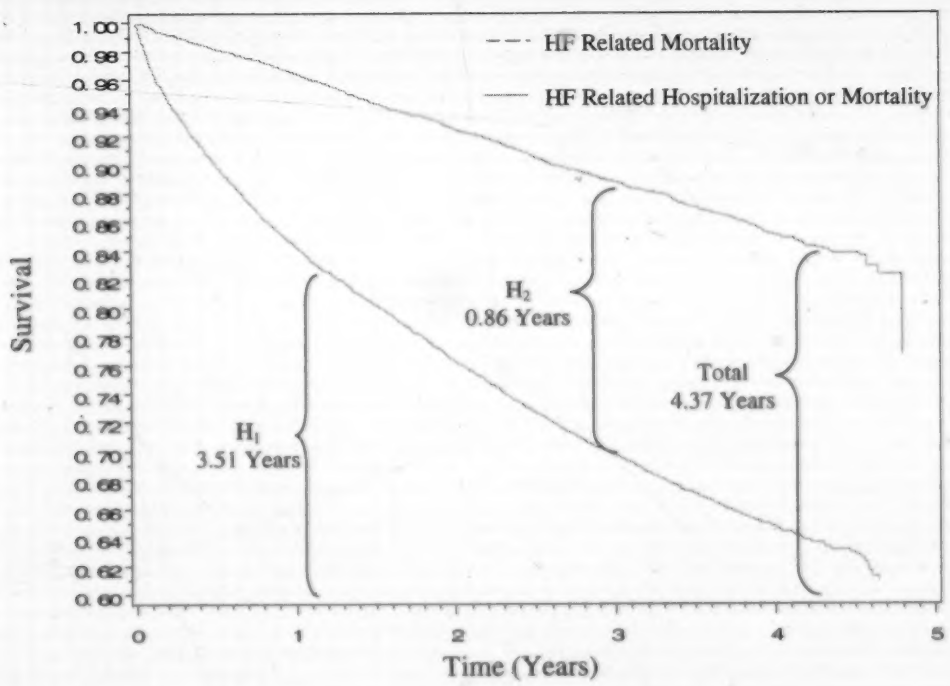


Table 5.5: Sensitivity analyses according to changes in utility coefficients

A. Metformin Study

Parameter varied	Group	Utility H_1	QALY H_1	Utility H_2	QALY H_2	Total QALYs	Difference in Total QALYs	Difference from Standard Analysis (%)
Base Case	Sulfonylurea	0.81	1.07	0.57	1.90	2.97	0.50	50
	Metformin	0.81	1.34	0.57	2.13	3.47		
H_1 increased 10%; H_2 base	Sulfonylurea	0.84	1.11	0.57	1.90	3.01	0.51	47
	Metformin	0.84	1.39	0.57	2.13	3.52		
H_1 decreased 10%; H_2 Base	Sulfonylurea	0.78	1.03	0.57	1.90	2.93	0.49	53
	Metformin	0.78	1.29	0.57	2.13	3.42		
H_1 base; H_2 increased 10%	Sulfonylurea	0.81	1.07	0.60	2.00	3.07	0.51	46
	Metformin	0.81	1.34	0.60	2.24	3.58		
H_1 base; H_2 decreased 10%	Sulfonylurea	0.81	1.07	0.54	1.80	2.87	0.49	53
	Metformin	0.81	1.34	0.54	2.02	3.36		
H_1 increased 10%; H_2 decreased 10%	Sulfonylurea	0.84	1.11	0.54	1.80	2.91	0.50	50
	Metformin	0.84	1.39	0.54	2.02	3.41		
H_1 decreased 10%; H_2 increased 10%	Sulfonylurea	0.78	1.03	0.60	2.00	3.03	0.50	49
	Metformin	0.78	1.29	0.60	2.24	3.53		
H_1 increased 10%; H_2 increased 10%	Sulfonylurea	0.84	1.11	0.60	2.00	3.11	0.52	43
	Metformin	0.84	1.39	0.60	2.24	3.63		
H_1 decreased 10%; H_2 decreased 10%	Sulfonylurea	0.78	1.03	0.54	1.80	2.83	0.48	57
	Metformin	0.78	1.29	0.54	2.02	3.31		

B. DIG Study

Parameter varied	Group	Utility H_1	QALY H_1	Utility H_2	QALY H_2	Total QALYs	Difference in Total QALYs	Difference from Standard Analysis (%)
Base Case	Placebo	0.81	2.61	0.57	0.62	3.23	0.10	42
	Digoxin	0.81	2.84	0.57	0.49	3.33		
H_1 increased 10%; H_2 base	Placebo	0.84	2.70	0.57	0.62	3.33	0.11	47
	Digoxin	0.84	2.95	0.57	0.49	3.44		
H_1 decreased 10%; H_2 Base	Placebo	0.78	2.51	0.57	0.62	3.13	0.10	37
	Digoxin	0.78	2.74	0.57	0.49	3.23		
H_1 base; H_2 increased 10%	Placebo	0.81	2.61	0.60	0.65	3.26	0.10	38
	Digoxin	0.81	2.84	0.60	0.52	3.36		
H_1 base; H_2 decreased 10%	Placebo	0.81	2.61	0.54	0.59	3.20	0.11	46
	Digoxin	0.81	2.84	0.54	0.46	3.31		
H_1 increased 10%; H_2 decreased 10%	Placebo	0.84	2.70	0.54	0.59	3.29	0.12	50
	Digoxin	0.84	2.95	0.54	0.46	3.41		
H_1 decreased 10%; H_2 increased 10%	Placebo	0.78	2.51	0.60	0.65	3.17	0.09	32
	Digoxin	0.78	2.74	0.60	0.52	3.25		
H_1 increased 10%; H_2 increased 10%	Placebo	0.84	2.70	0.60	0.65	3.36	0.11	43
	Digoxin	0.84	2.95	0.60	0.52	3.46		
H_1 decreased 10%; H_2 decreased 10%	Placebo	0.78	2.51	0.54	0.59	3.10	0.10	41
	Digoxin	0.78	2.74	0.54	0.46	3.20		

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CHAPTER 6: SUMMARY

6.1 Summary of Research

There is increasing interest in the scientific literature with respect to diabetes and heart failure. This has included the degree of comorbidity and associated outcomes, but more recently there has been considerable attention directed towards the potential impact of antidiabetic therapies in people with heart failure and diabetes. Previously, there was a paucity of evidence to guide clinicians as to the most appropriate therapeutic interventions to control blood glucose levels in people with comorbid heart failure and diabetes. Past recommendations have therefore been based on expert opinion, pathophysiological rational or clinical experience. To address this information gap, several interrelated studies were undertaken to enhance knowledge in this area.

The specific objective of this program of research was to systematically evaluate the effects of antidiabetic agents on morbidity and mortality in patients with diabetes and heart failure, with particular attention directed towards the benefits and/or harm associated with metformin therapy. This objective was accomplished through three different, but related, studies. In carrying out this clinical research, a second major outcome was the development of a methodological technique that may improve the validity and interpretation of composite outcomes commonly used in observational and randomized controlled trial research such as we conducted in our research.

Historically, the use of metformin therapy in patients with heart failure was considered 'inappropriate'.[1-3] Given the benefits observed with metformin in other patient populations[4], it is not surprising that metformin therapy is increasingly being used in patients with heart failure, despite limited evidence of efficacy or safety. Initial observational evidence from Masoudi *et al.* had suggested that metformin therapy maybe associated with improved outcomes in people with heart failure and diabetes.[5] It remained uncertain, however, if the observed benefits of metformin therapy truly existed or was an artifact of the patient population studied or the relatively short duration of follow-up. Importantly, we were able to extend these beneficial finding of metformin therapy to a much boarder population of patients with diabetes and heart failure. In our initial observational study[6], metformin therapy was associated with clinically and

statistically significant reductions in morbidity and mortality in both the short and longer term, as compared to sulfonylurea therapy. Furthermore, metformin therapy was not associated with any increase in measurable harm, which is in contrast to the historical viewpoint of metformin use in patients with heart failure.

Recognizing the mounting evidence for the use of antidiabetic agents in patients with heart failure and diabetes, our second study was a systematic review and meta-analysis. Despite the concern surrounding antidiabetic agent use in this population, our review identified few studies that had systematically evaluated the effects of antidiabetic agents on morbidity or mortality in patients with heart failure and diabetes. Of the available evidence, insulin therapy was associated with a marked increased risk of mortality in patients with heart failure in 3 of the four studies evaluated. In contrast, both metformin and thiazolidinedione therapy was associated with reductions in mortality compared to other antidiabetic therapies. Although a meta-analysis was intended, significant statistical heterogeneity precluded formal pooling of studies results, highlighting the continued lack of clear evidence directing clinical practice.

In addition to the beneficial effects of metformin on mortality, individual studies also suggested metformin maybe associated with reduce morbidity (i.e., hospitalizations), which was confirmed by formal pooling of study results. These benefits did not seem to extend to the thiazolidinediones. There has been concern in the literature as the potential effects of thiazolidinedione therapy on the development and progression of heart failure. Although only two studies evaluated the potential effects of thiazolidinedione therapy on heart failure related hospitalizations, both suggested a small increased risk, which was confirmed with formal pooling of study results.

Based on our systematic review and meta-analysis, of the therapies available to control blood sugars in people with heart failure, only metformin therapy was not associated with any measurable harm. These results are in stark contrast to many opinions in the literature suggesting metformin is potentially harmful in patients with heart failure. Importantly, however, in all of the studies included in the systematic review and meta-analysis, no study specifically randomized patients to different antidiabetic agents. Due to the observational nature of all the studies, it is possible that the results are due to selection bias and/or confounding by disease severity.

In an attempt to overcome the limited evidence for the use of metformin in patients with heart failure, we designed and implemented the PHANTOM (Patients with Heart Failure ANd Type 2 Diabetes Treated with Placebo Or Metformin) pilot study, to evaluate the feasibility of a large randomized controlled trial of metformin in patients with heart failure and type 2 diabetes. Although 100 subjects with heart failure and diabetes were proposed to be included in the pilot study, screening of 58 consecutive patients did not result in any potential study candidates. Due to the poor availability of suitable patients, the pilot study was stopped.

Although no patients were enrolled, several interesting results were obtained in conducting the PHANTOM pilot study. Overall, a high number of individuals with heart failure and diabetes were excluded for an A1c <7% and for using high dose metformin, both of which were unanticipated during the design of the pilot study. In fact, metformin was the most commonly prescribed oral antidiabetic agent, with over 50% of subjects with diabetes and heart failure being prescribed metformin, despite its contraindication.

Based on our experience with the PHANTOM pilot study, we concluded it is unlikely a randomized controlled trial of metformin use in heart failure could be completed in our setting in the near future. Therefore, the final objective of this research program was aimed at improving analyses and interpretation of evidence from observational studies. In particular, we were interested in the use and interpretation of composite outcomes of mortality and hospitalization, commonly used in clinical research for heart failure. To this end, we reanalyzed our previously reported observational study of metformin use in patients with heart failure and diabetes. We adapted a methodology previously employed in the area of oncology research, which incorporates health-related quality of life into survival analyses. By doing so, we demonstrated how quality adjusted survival analysis can adjust for the potential unequal impact of the components of the composite outcome on a patients' health.

To further illustrate the versatility of the method, we also applied this quality adjusted survival analysis to data from a previously published randomized controlled trial in heart failure, the DIG Study. In both our observational study of metformin in patients with heart failure and diabetes and in the DIG study, the quality adjusted survival analysis resulted in estimates which were clinically and significantly different as

compared to conventional survival analyses. We concluded that the incorporation of health-related quality of life into survival analyses reduces bias associated with the use of composite outcomes used in both observational and clinical trial research. As a result, the true benefits or harm associated with a therapeutic intervention may be more easily identified. Furthermore, quality adjusted survival is directly compatible with many economic evaluation methods, thereby potentially providing better economic estimates of therapeutic interventions.

6.2 Implications for Practice

Hyperglycemia is a strong independent risk factor for the development of heart failure. Although the true impact of controlling hyperglycemia in patients with heart failure remains uncertain, the beneficial effects of tight glycemic control would be expected to be extend to patients with heart failure.[7] Although sulfonylurea therapy has been commonly used in the treatment of hyperglycemia in patients with heart failure, there is increasing concern with the use of these agents in patients with ischemic conditions[8], which is often seen in patients with heart failure. Whether this is related to the increasing use of metformin in patients with heart failure is unknown; however, the fact remains that metformin use has increased in patients with heart failure, despite the contraindication.

Given the increasing evidence for the use of metformin, numerous researchers have questioned the contraindication of metformin in patients with heart failure and we believe rightfully so. Metformin is equipotent with other antidiabetic agents in reducing blood glucose levels, either alone or in combination with other antidiabetic agents.[4,9] Moreover, metformin has also been shown to improve mortality in patients with diabetes.[4,10]

The additional evidence generated through the series of studies in this research program strongly suggests that many of the concerns with using metformin in patients with heart failure may be unfounded. Both our observational study and the systematic review of the literature suggests that metformin maybe the only agent not associated with measurable harm in patients with heart failure, and in fact, maybe associated with

substantial reductions in both morbidity and mortality. Furthermore, results of our pilot study suggest that many clinicians also believe the contraindication is unfounded and are using metformin as an important component of the glucose lowering regimen in patients with heart failure.

Our program of research provides important evidence for the front line clinician who is initiating or modifying antidiabetic regimens. Like other authorities[11,12], we believe that the currently available evidence indicates that the contraindication of metformin use in patients with pharmacologically managed heart failure and diabetes is unwarranted and that product labelling of metformin therapy should be re-evaluated. Furthermore, based on the available evidence, metformin therapy should be considered as the preferred antidiabetic therapy in patients with heart failure.

Our research also highlights the need for new methodologies in clinical research to provide a clearer picture of the potential benefits or harm associated with therapeutic interventions. There are an increasing number of pharmacological agents available to clinicians to control diabetes. In most cases, the benefits of one therapy versus another are often small. Moreover, there is often a 'trade-off' between benefits and side effects among different therapeutic agents and it is often difficult to determine where these differences exist. Further complicating interpretation is the fact that most studies rely on composite outcomes in their assessment. Composite outcomes may lead to biased results which may over- or under-estimate treatment benefits. As a result, the true impact on the patients' overall health is rarely known. Methods, such as the quality adjusted survival analysis, may be able to provided additional information to help better inform patients, clinicians, and policy makers, ultimately leading to better informed treatment decisions.

6.3 Implications for Future Research

While our research improved the level of evidence on how to best control hyperglycemia in patients with heart failure and diabetes, additional research and evidence in this area could further our understanding. A key limitation of our research is the reliance on data from observational sources, thus a randomized controlled trial of

antidiabetic agents, including metformin and thiazolidinediones, in patients with heart failure and diabetes would be ideal.

As we noted in our PHANTOM pilot experience, it is unclear if sufficient clinical uncertainty exists to adequately address these issues through a randomized control trial. Clinicians are increasingly being asked to direct patients into clinical trial research. It is therefore imperative that the clinician be convinced that the resulting trial will provide a major advancement in the treatment of the disease.[13] Further adding to the difficulties of completing a successful clinical trial is the fact that clinical trials generally lag considerably behind current treatment practice. Clinicians must formulate a treatment plan for patients generally well in advance of any clinical trial evidence, often based on a number of small individual studies, expert opinion, or clinical experience. As seen in other areas, clinical practice may be difficult to change, even with the publication of a successful clinical trial.[14]

On the surface, the case of using metformin in patients with heart failure appears to be affected by all of these issues. Our pilot data suggested that a large majority of clinicians are already using metformin in patients with heart failure. As a result, clinical uncertainty does not appear to exist. In fact, in developing the protocol for the PHANTOM pilot study, one clinician felt strongly that it was unethical to withhold metformin in patients with heart failure. A limitation identified with our pilot is the potential generalizability to other settings outside of Capital Health Region in Alberta. It may be that clinicians in other jurisdictions might have a different level of uncertainty regarding metformin use in this patient population. Furthermore, given the frequent use of metformin, akin to shutting the barn doors after the horses have bolted, it may be that such a trial is unlikely to change clinical practice. Irrespective, it is important that the best available evidence be generated for the use of antidiabetic agents in patients with heart failure and diabetes. As a result, a randomized control trial, perhaps in a different clinical setting, could still be pursued in future research.

Another avenue of future research should also be directed towards improving the use and interpretation of composite outcomes in clinical research to patients, clinicians, and policy makers. We have introduced a new methodological technique that may facilitate this. Several outstanding limitations exist with this method, however, including

the incorporation of multiple events into the quality adjusted survival analysis and the impact of different health states in people with heart failure and diabetes. Despite the common occurrence of heart failure and diabetes, there is limited evidence for the impact of a hospitalization on a person's health related quality of life in people with heart failure. Moreover, there is little evidence on the specific impact of antidiabetic therapies on the health-related quality of life for people with heart failure and diabetes. These are outstanding issues which should garner future attention.

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